Mechanisms of immune regulation in allergy

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EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

GLOBAL ATLAS OF ALLERGY

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Allergy - Mechanisms

Epidemiology and risk factors

Allergy diagnosis

Major Allergic Diseases

Other hypersensitivity diseases

Special considerations

Management of allergic diseases

Towards a comprehensive global strategy for the management of allergic diseases

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Editors

Cezmi A. Akdis

Ioana Agache

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PREFACE

Allergic diseases are affecting the lives of more than one billion people worldwide. With an epidemic rise during the last 60 years, their prevalence is expected to reach up to 4 billion in 2050s. Because of immense numbers of affected individuals, the general public confronts huge direct and indirect costs with major effects on macroeconomics due to health-care, loss of productivity and absenteeism of patients. Unfortunately, high number of unmet needs due to missing scientific knowledge in disease mechanisms, prevention, patient care, and social determinants remain to be resolved.

To tackle this huge global health problem, we as the EAACI decided to develop the "Global Atlas of Allergy" as a follow up of our "Global Atlas of Asthma" which was launched last year. With this Atlas, we aimed to gather evidence to call attention to the burden of allergic diseases; to warrant their recognition as a main concern in national health strategies; to reveal their priority for research; to describe environmental factors; to evaluate the best ways to prevent and control allergies; to provide guidance on how to overcome barriers; to alert the political bodies to ensure global management approaches.

The EAACI Global Atlas of Allergy contains 139 chapters written by 183 authors with 274 illustrations and 100 tables. It is developed as a desktop reference for multisectoral usage covering all aspects of allergic diseases from allergens, epidemiology, risk factors and molecular and cellular mechanisms to their management, major current problems in allergies and associated diseases, prevention and control of allergic diseases. In addition, the Atlas will offer an educational tool and a desktop reference for medical students, allied health workers, primary care physicians, medical industry, policy makers, patient organizations and specialists dealing with allergies and co-morbid diseases. We would like to thank all of the authors for their contributions.

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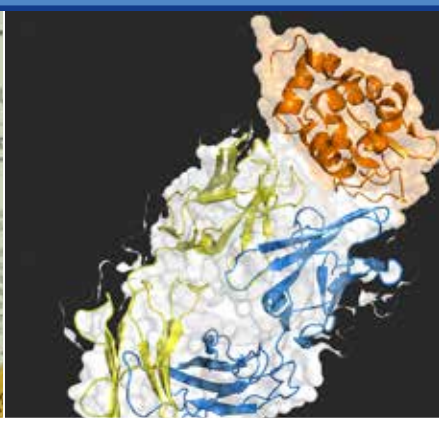
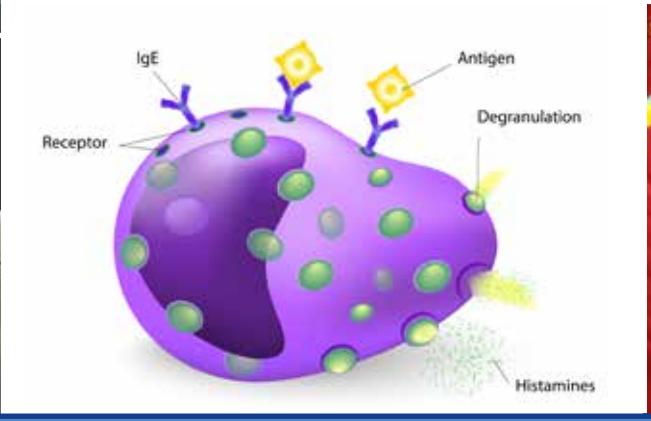
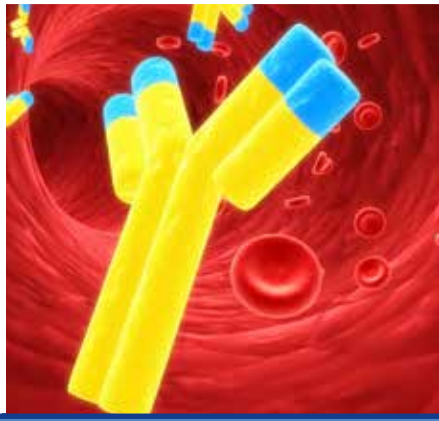
Section A







ALLERGY - MECHANISMS

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* Allergens: structure and function; mechanisms of allergenicity; allergens and cross-reactivity; house dust mite allergens; pet allergens; tree pollen allergens; grass pollen allergens; weed pollen allergens; food allergens; venom allergens; emerging allergens; pollen allergens and geographical factors
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* Immunoglobulin E and other antibodies in allergy
* Role of superantigens in allergic diseases
* Cytokines in allergy
* Cell migration and chemokines
* Complement-mediated regulation of the allergic response
* Lipid mediators of hypersensitivity and inflammation
* Lipid mediators in resolution of allergic inflammation
* Allergy and the epithelial barriers
* Epithelial proteases and allergic diseases
* Mechanisms of immune regulation in allergy
* Neuro-immune regulation of allergic inflammation
* United airways and immune regulation
* Genetics of allergy
* Epigenetics of allergy
* Endotypes of allergic diseases
* Animal models of allergic disease

1 WHAT IS ALLERGY

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The term "Allergy" was born on July 24, 1906 in the Münchener Medizinische Wochenschrift as "specifically altered reactivity of the organism". Today, we define allergy as immunological hypersensitivity that can lead to a variety of different diseases via different pathomechanisms and thus different approaches in diagnosis, therapy and prevention can be taken. (Table 1). Several misconceptions can be delineated (Table 2).

KEY MESSAGES

- The term "Allergy" was first coined on July 24, 1906 as "specifically altered reactivity of the organism
- Today, we define allergy as an immunologically-mediated and allergen-specific hypersensitivity
- Allergies can be seen in almost every organ, most commonly in the skin and the mucous membranes
- Allergology is the science regarding allergic diseases and their differential diagnoses and mechanisms


MÜNCHENER
MEDIZINISCHE WOCHENSCHRIFT.
No. 29. 24. Juli 1906.
53. Jahrgang
Originalien
Allergie.
Von C. v. Pirquet.

Figure 1 The word "allergy" first appeared on July 24, 1906 in the Münchener Medizinische Wochenschrift in an essay written by Clemens von Pirquet, a pediatrician from Vienna. (*Reproduced with permission from Ring J: Allergy in Practice. Springer Berlin, Heidelberg, New York, 2005.*)

Allergology is the science regarding allergic diseases and their differential diagnoses and mechanisms. It requires clinical experience in allergic diseases, basic understanding of the immune system in physiology and pathology and finally extensive knowledge of environmental factors in eliciting or modulating allergic reactions.

Allergy is not a disease itself, but a mechanism leading to disease. In clinical practice, allergy manifests in form of various different conditions such as anaphylaxis, urticaria, angioedema, allergic rhinoconjunctivitis, allergic asthma, serum sickness, allergic vasculitis, hypersensitivity pneumonitis, atopic dermatitis (eczema), contact dermatitis and granulomatous

TABLE 1

Definitions of terms frequently used in allergy	
Sensitivity	Normal response to a stimulus
Hypersensitivity	Abnormally strong response to a stimulus
Sensitation	Development of increased sensitivity after repeated contact
Allergy	Immunologically mediated hypersensitivity leading to disease
Anaphylaxis	severe, life-threatening, generalized or systemic hypersensitivity reaction

TABLE 2

The most common misconceptions of allergy
• natural reaction
• a symptom or sign (e.g. rhinitis)
• incompatibility of toxic/irritant substances (e.g. tobacco smoke)
• psychological aversion
• incurable

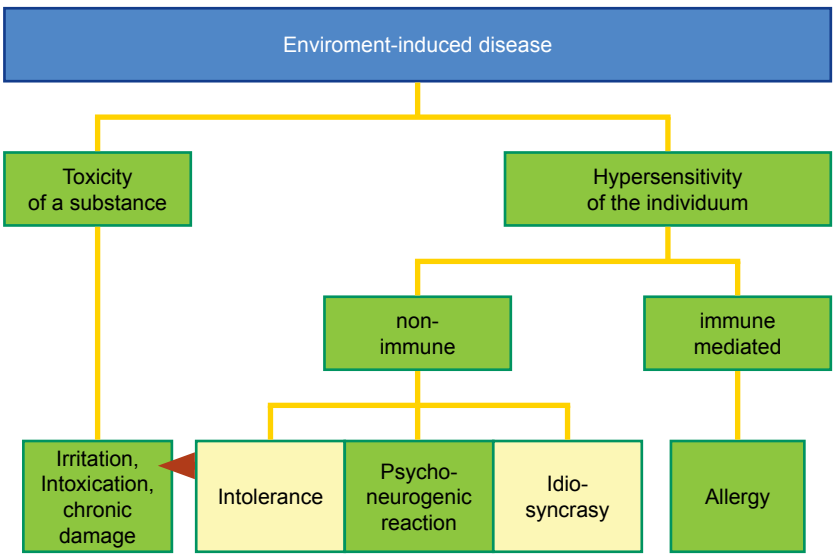

Figure 2 Classification of environmentally related health these disorders. (*Reproduced with permission from Ring J: Allergy in Practice. Springer Berlin, Heidelberg, New York, 2005.*)

reactions, as well as the colorful spectrum of food- or drug – induced hypersensitivity reactions. Allergies can be seen in almost every organ. Most commonly, however, it is the skin and the mucous membranes that are involved since they represent the frontier between the individual organism and its environment.

Allergy often starts in the first three months of life but very rarely at birth, although there is a strong genetic background. Allergy in some cases does not persist over life-time; it starts and some patients may out grow their allergic disease spontaneously. We should study these patients intensively, who spontaneously lose their allergy. Many allergic diseases have a chronic course, but there are ways to cure. Allergic diseases can be influenced by psychological processes in a positive or in a negative way.

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2 THE DISCOVERY OF IgE

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Allergic asthma and rhinitis were already recognized in the 19th century, but the mechanisms behind the diseases were not understood. In 1919 Ramirez noticed that blood transfusion could transfer allergic asthma and passively sensitize the recipient. In 1921, Prausnitz and Küstner demonstrated passive sensitization of the skin, since then referred to as the PK-test.

The search for reagin, the factor in plasma causing the positive PK-test, was unsuccessful for about 45 years and some rather confusing proposals were published, e.g. identifying reagin as IgA. In the 1960's K. and T. Ishizaka published several articles describing an antiserum that could block the PK-test indicating that it reacted with reagin. They referred to this antiserum as anti-γE. Not surprisingly considering the very low serum concentration of IgE, they did not succeed in isolating their γE.

In 1965 S.G.O. Johansson in Uppsala detected in the serum of a myeloma patient an M-component that could not be identified as any of the 4 known immunoglobulin classes. Working with H. Bennich, the unique immunological and physicochemical characteristics

KEY MESSAGES

- In 1921, Prausnitz and Küstner demonstrated passive sensitization of the skin, since then referred to as the PK-test
- In the 1960's K. and T. Ishizaka published several articles describing an antiserum that could block the PK-test indicating that it reacted with regain
- In 1965 S.G.O. Johansson in Uppsala detected in the serum of a myeloma patient an M-component that could not be identified as any of the 4 known immunoglobulin classes
- The discovery of IgE and the understanding of the IgE-mediated inflammation, allergic asthma and rhino-conjunctivitis, food allergy and eczema has had a significant impact on diagnosis and treatment of allergy

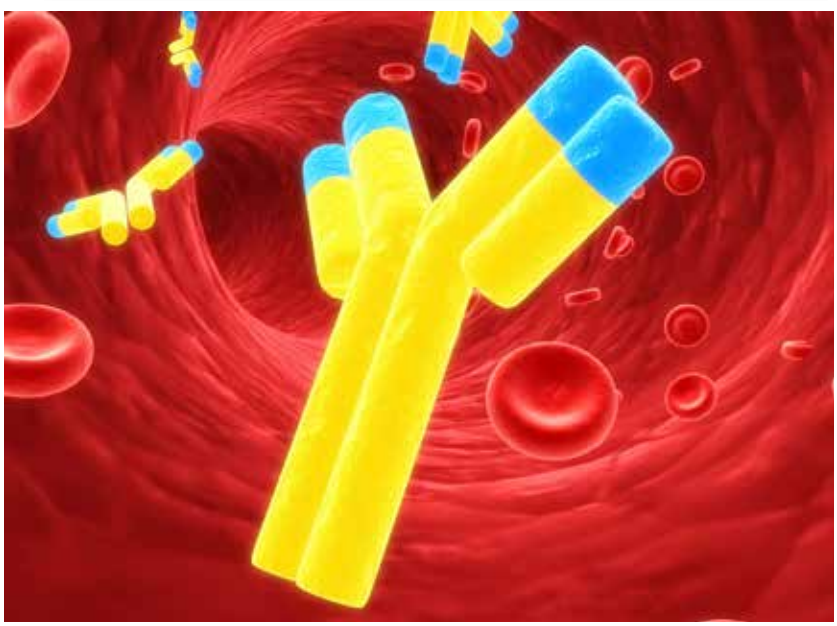

Figure 1 From left L. Wide, H. Bennich and S.G.O. Johansson presenting RAST in 1974.

of the new immunoglobulin, provisionally labelled IgND after the initials of the patient, were documented and published. Very small amounts of IgND did, in dose-response, block the PK-test and the active structure was located in the Fc-fragment. A sensitive radio-immuno assay was developed for IgND. Extremely low serum concentrations, in the order of a few nanograms per ml, were found in healthy individuals but, interestingly, 10-100 fold higher levels were found in allergic individuals.

Purified IgND was sent to the Ishizakas in 1967 and was found to react with their anti-γE. In February 1968 the WHO International Reference Centre in Lausanne, where studies on IgND had been performed for some months, invited the two groups to a meeting to review comparative laboratory studies of IgND and γE, resulting in the publication of the official report on the fifth immunoglobulin class, IgE.

The discovery of IgE has had a significant impact on the diagnosis and management of allergic disease, enabling clinicians to differentiate between IgE-mediated allergic diseases and other hypersensitivity reactions, and to manage allergic diseases according to their underlying mechanisms. Tests became available that allowed a more simple and reliable diagnosis covering a very broad spectrum of allergens. The characterization and standardization of allergen preparations for clinical diagnosis and allergen specific immunotherapy, ASIT, improved although there is still much to do in this area. An injectable monoclonal anti-IgE is now available that eliminates IgE and has an important role in the management of severe allergic asthma, severe food allergy and chronic urticaria.

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3a ALLERGENS – STRUCTURE AND FUNCTION

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Patients with type I allergy make IgE antibodies against some, but not against all environmental or dietary proteins they are exposed to. In fact, most allergens belong to a rather limited number of protein families.

Can we identify common structural or functional properties of proteins that turn them into allergens? Before answering this question, it is important to clearly define what an allergen is. An absolute prerequisite for a molecule to be designated an allergen is for it to bind specific IgE antibodies. Not every protein fulfilling that requirement is however also capable of instructing the immune system to start producing these IgE antibodies, i.e. of being a primary sensitizer (Figure 1). Clear examples of allergens not able to do so are those in fruits, nuts and vegetables that are cross-reactive with the major birch pollen Bet v 1. Their allergenicity is dependant on their structural (and functional) similarity to their "parent" molecule Bet v 1, the primary sensitizer.

The more intriguing question is however, what determines whether a protein is capable of being the primary sensitizer. The answer to this question is complex, because potential endogenous pro-allergenic properties of a protein cannot be seen in isolation from the individual being exposed and from the context of exposure, which includes timing and dose of exposure, and the presence of co-factors that may act as pro-allergenic or anti-allergenic adjuvants (Figure 2).

KEY MESSAGES

- A protein capable of instructing the immune system to start producing IgE antibodies is called a primary sensitizer
- Pro-allergenic properties of a protein cannot be separated from the individual being exposed or from the context of exposure
- Several structural and functional properties have been identified that contribute to allergenicity
- There is not a single common denominator for allergenicity

With that in mind, are there common endogenous structural or functional properties that determine allergenicity? Glycosylation per se has often been mentioned as marker for allergenicity, but convincing evidence for such a general claim cannot be found. Some properties of proteins, including specific types of glycosylation and binding of lipids, seem to determine their role as allergens via interaction with the innate immune system. Many known allergens are indeed lipid binding proteins (e.g. Bet v 1 and homologues, house dust mite group 2 allergens, lipocalins of pets, plant lipid transfer proteins), and some are glycoproteins (e.g. peanut Ara h 1 and grass pollen Phl p 1). Their lipid ligands and conjugated glycans have been shown to interact with pathogen recognition receptors such as Toll-like receptors and C-type lectins on antigen-presenting cells, thereby skewing the immune systems towards Th2-type responses and IgE production (Figure 3). In addition, protease activity such as of the cysteine protease Der p 1 has been shown to drive Th2 inflammation. It is important to note that all these innate Th2-skewing properties may also turn other proteins without these pro-allergenic properties

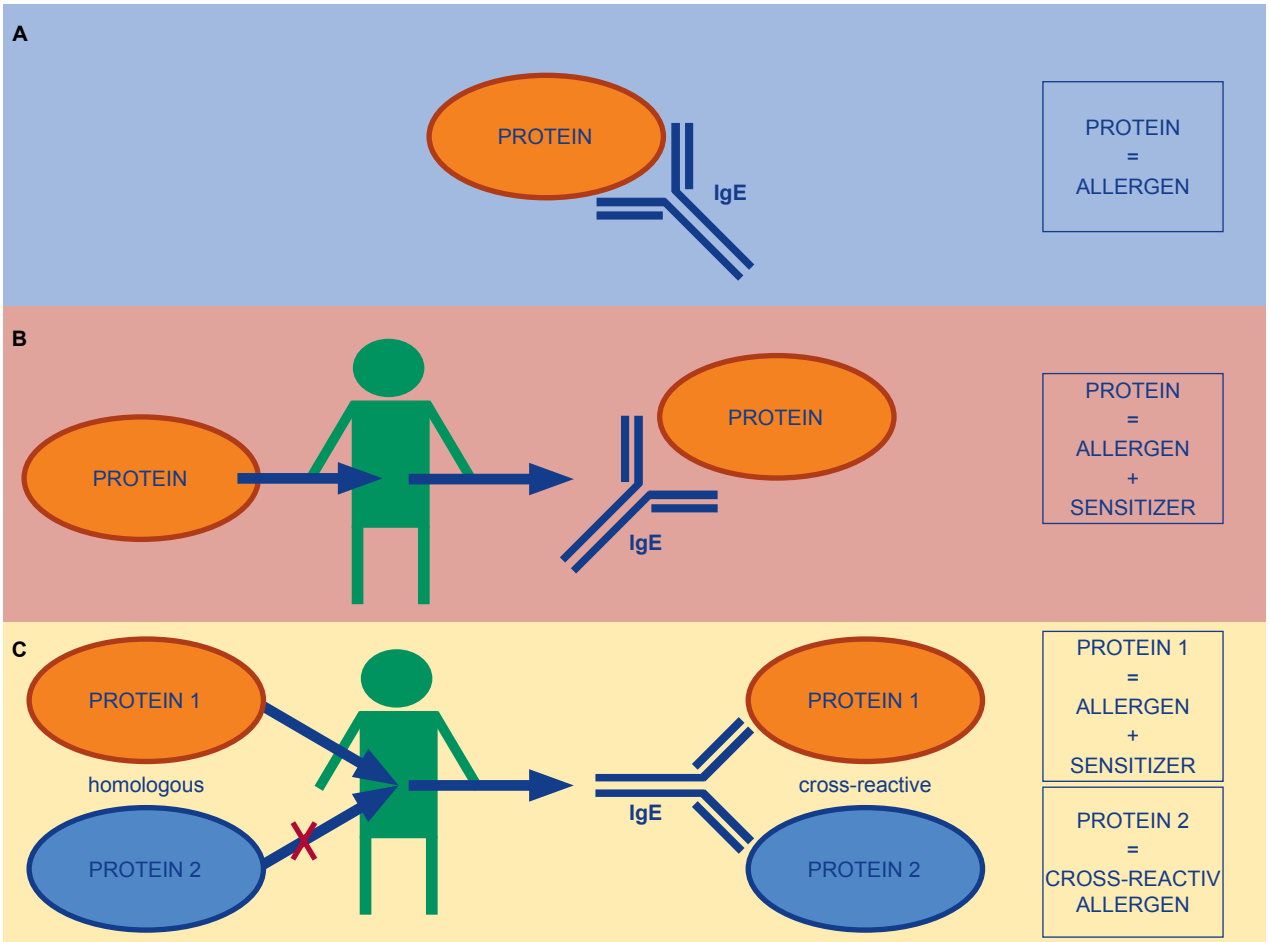

Figure 1 Panel A illustrates the minimum requirements for a molecule to be designated as an allergen: it binds IgE antibodies Panel B and C depict the two identities an allergen can have: it can itself act as primary sensitizer (orange in panel B and C), or it cannot and binds IgE only based on cross-reactivity with the primary sensitizer (blue in panel C).

into allergens during simultaneous exposure.

In summary, several structural and functional properties have been identified that contribute to allergenicity, but it is safe to say that there is not a single common denominator for allergenicity.

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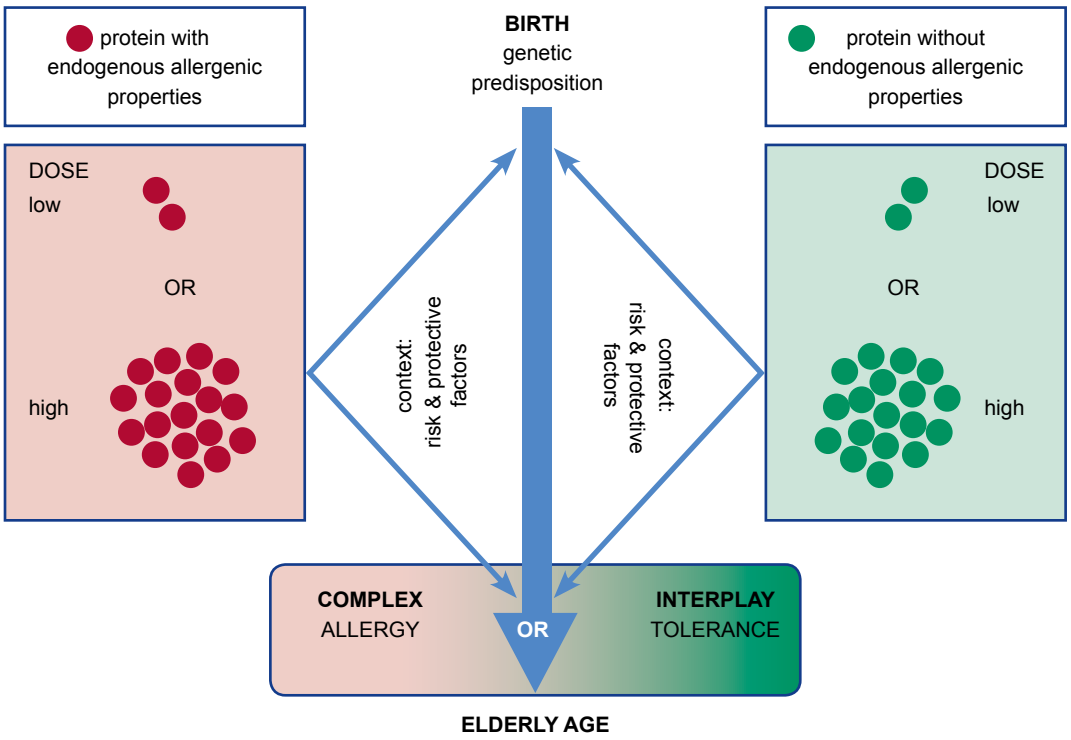

Figure 2 Sensitization is a complex interplay of the individual exposed (inherited risk of becoming allergic), the timing of exposure (earlier in life the immune system is more susceptible to sensitization but also to induction of tolerance), the dose (high early life exposure may skew towards tolerance), the context of exposure (environmental exposures such as pollution, microbes, parasites, diet, lifestyle) and endogenous properties of the protein.

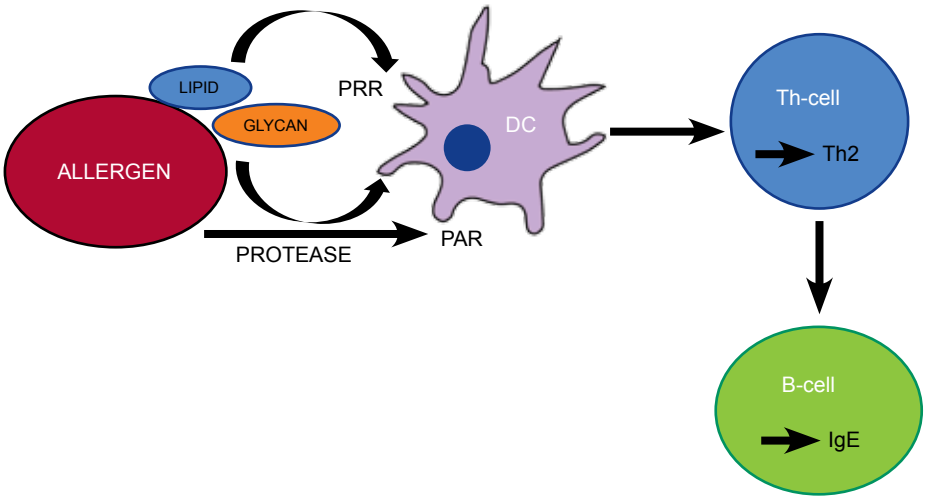

Figure 3 Allergens can interact via various mechanisms with dendritic cells skewing them towards a DC2 phenotype, which in turn skews adaptive immunity towards Th2 and IgE production.

3b

MECHANISMS OF ALLERGENICITY OF ALLERGENS

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KEY MESSAGES

- The innate immune system plays a fundamental role in shaping the response to potentially allergenic proteins
- Allergic sensitization, a multifactorial process, is influenced by a protein's biological and molecular features and by the interaction pathway/s with the immune system
- Proteins interact with Toll-like-, C-type lectin-, NOD-like-, and protease-activated receptors (present on epithelial cells and dendritic cells) or with surfactant proteins (present in soluble form) to manifest their allergenicity
- Lipids (directly bound by allergens, present in the allergen source, or originating from microbial contaminations) modulate the immune response of predisposed individuals by interacting with the innate immune system

Allergens interact with various parts of the innate immune system which plays a fundamental role in shaping adaptive immune responses (Figure 1). The innate immune system comprises several cell types that express pattern recognition receptors (PRRs). PRRs recognize pathogen- or damage-associated molecular patterns (PAMPs, DAMPs) which frequently accompany allergens.

MEMBRANE-ASSOCIATED, CYTOPLASMIC AND SOLUBLE PRRS

Toll-like receptors (TLR) are a conserved family of PRRs. The allergens Der p 2 (house-dust mite), Fel d 1 (cat), and Can f 6 (dog) bind lipopolysaccharide (LPS) and interact with TLR4, shifting the LPS-response curve to a Th2-inducing range. Bacterial contaminations present on pollen, shown for ryegrass and *Parietaria*, are responsible for triggering TLR2, TLR4 and TLR9 signaling. C-type lectin receptors contain carbohydrate recognition domains that bind glycosylated allergens and trigger pathways that determine T-cell polarization. Ara h 1 (peanut), Der p 1 (house dust mite) and Can f 1 (dog) interact with the C-type lectin receptor DC-SIGN; Ara h 1, Der p 1 and 2, Fel d 1, Can f 1 and Bla g 2 (cockroach) with the mannose receptor. Protease-activated receptors (PARs) signal in response to extracelluar proteases. Allergens of house dust mite (Der p 1, -3, -9) and mold (Pen c 13) activate PAR-2 and induce IL-25 and thymic stromal lymphopoietin (TSLP).

NOD-like receptors (NLRs) sense cytoplasmic PAMPs and DAMPs. Some NLRs are core components of *inflammasomes*, protein complexes involved in generating the pro-inflammatory cytokines IL-1β and IL-18. Inflammasomes are triggered by Der p 1, Api m 4 (bee), and *Ambrosia artemisiifolia* pollen extracts.

Surfactant associated proteins (SP), found in the alveoli of the lungs, bind inhaled glycosylated allergens via a carbohydrate recognition domain. Der p 1 and Der f 1 degrade SP-A resulting in increased degranulation of mast cells and basophils triggered by these allergens.

CELLS OF THE INNATE IMMUNE SYSTEM

Epithelial cells function as physical barrier whose tight junction proteins are degraded by proteases including Der p 1 and Act d 1

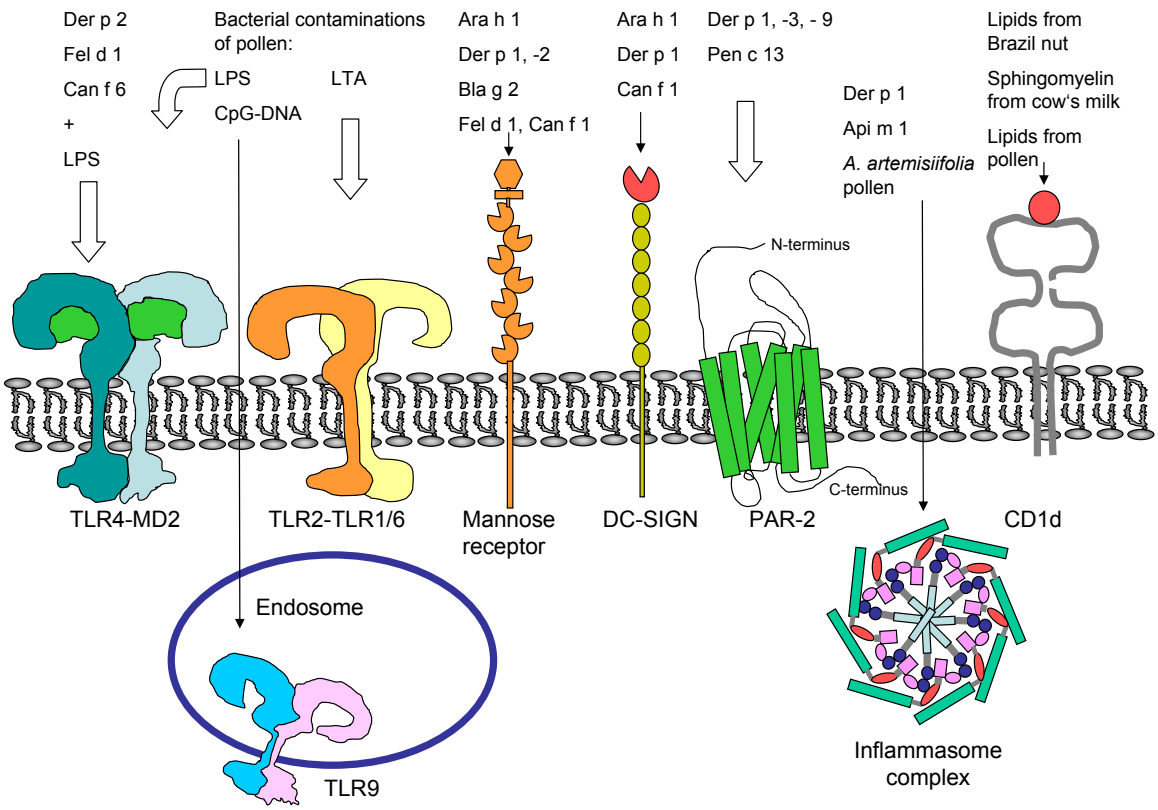

Figure 1 Simplified model of innate immune mechanisms activated by allergens. Examples are given for interactions of allergens with Toll-like receptors (TLRs) via binding by the allergen or co-delivery of bacterial compounds (LPS: lipopolysaccharide. LTA: lipoteichoic acid); with C-type lectin receptors via carbohydrate moieties present on allergens; with protease-activated receptor (PAR) 2 via the allergens' proteolytical activity; and with inflammasome complexes (2-4). In addition, the presentation of lipids from the allergen source by CD1d to invariant natural killer T cells, which enhances sensitization or in some cases even drives it, is shown.

(kiwi). Following allergen contact, epithelial cells produce TSLP, IL-25 and IL-33 and instruct dendritic cells to induce Th2 responses. Dendritic cells bridge innate and adaptive immunity and polarize the T helper cell response (5). Polarization towards a Th2 response in dendritic cell-T cell co-cultures has been shown for Bet v 1 (birch pollen) and Pru p 3 (peach) when cells were derived from allergic donors. Invariant natural killer T cells (iNKTs) recognize lipids presented by CD1d (6). They secrete IL-4, -5 and -13 when presented lipids from Brazil nut or sphingomyelin from milk. Co-delivery of certain lipids and potentially allergenic proteins determine the outcome of the sensitization process.

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3c

ALLERGENS AND CROSS-REACTIVITY

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KEY MESSAGES

- Members of the same protein family may share IgE and T cell epitopes, which can cause allergic reactions by cross-reactivity
- Shared IgE epitopes between inhalant allergens and food allergens can induce an immediate IgE-mediated reaction confined to the oral cavity, known as the oral allergy syndrome
- Cross-reactivity at the T cell level represents one of the mechanisms of worsening of atopic eczema in birch-pollen allergic patients
- Immunological cross-reactivity is explored as a possible cure for allergy, by inducing cross-reactive regulatory T cells and/or cross-reactive blocking IgG4 antibodies

Allergens belong to a relatively low number of different protein families according to intrinsic features, e.g. similar amino acid sequences and/or 3-dimensional folding. Members of the same protein family may share IgE and T cell epitopes, which by cross-reactivity can cause allergic reactions. In this context, birch pollen-related food allergy has been well studied. This special form of food allergy affects more than 70% of birch pollen-allergic patients and is one of the most frequent food allergies in adults.

Bet v 1, the single major birch pollen allergen belongs to the pathogenesis-related protein family 10 and homologous molecules are present in various foods, e.g. Mal d 1 in apple, Pru av 1 in cherry, Gly m 4 in soy and Ara h 8 in peanut. Although these proteins derive from plant species non-related to birch trees, their primary and tertiary structures are highly homologous with Bet v 1.

Bet v 1 contains mainly conformational IgE-epitopes, as destruction of its 3-dimensional structure leads to a dramatic reduction of its IgE-binding capacity. Due to similar protein folding, Bet v 1 - homologs contain surface patches forming epitopes that may be recognized by Bet v 1 - specific IgE antibodies (Figure 1A). Although not all IgE-epitopes are shared, Bet v 1 - related food allergens contain sufficient epitopes to achieve cross-linkage of IgE bound to the surface of mast cells and basophils. In most cases, this induces the oral allergy syndrome, an immediate IgE-mediated reaction confined to the oral cavity. Destruction of the 3-dimensional protein structure, e.g. by gastrointestinal degradation or heat processing, reduces IgE cross-reactivity, which explains why cooked foods containing Bet v 1-related proteins usually are tolerated by birch pollen-allergic patients.

Cross-reactivity at the T cell level depends on amino acid sequence homologies. After uptake by antigen-presenting cells, allergens are degraded into short linear peptides, which are then loaded onto MHC class II molecules to be presented to T cells (Figure 1B). Proteins with homologous amino acid sequences are processed in analog fashion resulting in similar peptides. These activate cross-reactive T cells to proliferate and produce cytokines. Clinically, T cell activation by Bet v 1-related food allergens may result in a worsening of atopic eczema in birch pollen-allergic patients.

The analysis of the immune mechanisms underlying birch pollen-related food allergy has markedly

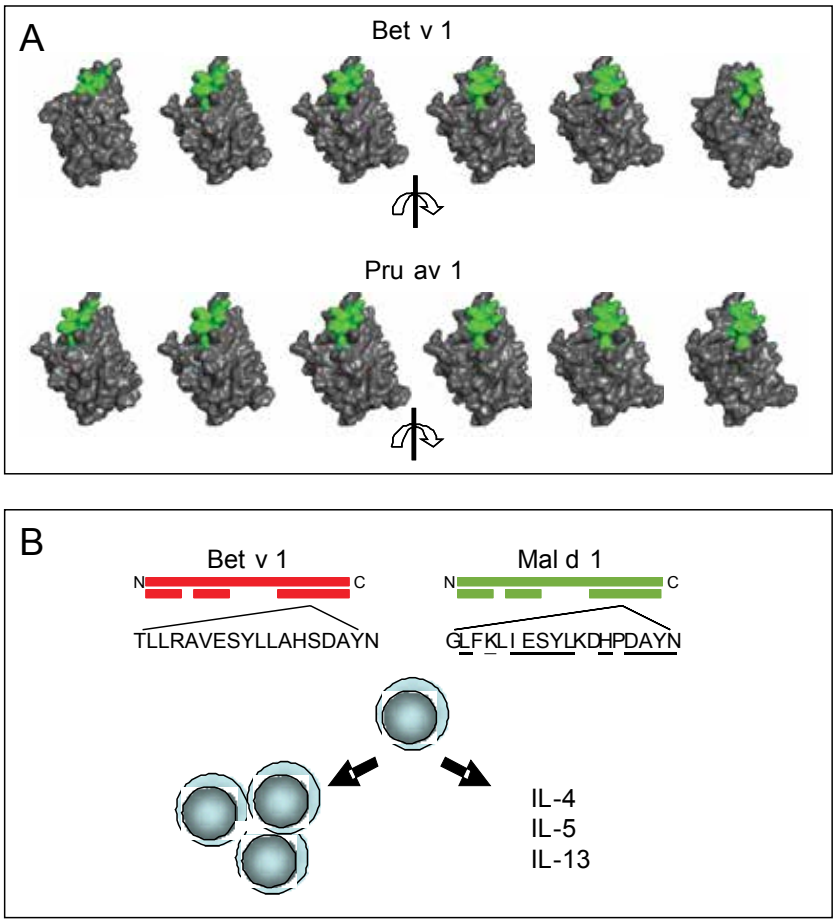

Figure 1 A. Homologous conformational epitopes cause IgE cross-reactivity. A putative IgE epitope defined on Bet v 1 and Pru av 1, the Bet v 1-homolog in cherry is shown in green (3). Protein models (pdb 1BV1 and 1E09, respectively) are displayed using Polyview3D. B. Homologous linear epitopes cause T cell cross-reactivity. Proteins with similar amino acid sequences (indicated as red and green lines) are processed in a similar manner by antigen-presenting cells leading to the generation of linear peptides. The highly cross-reactive C-terminal immunodominant T cell epitope of Bet v 1 and the homolog peptide of Mal d 1 are shown (4). Identical amino acid residues are highlighted in bold, similar residues are underlined. T cell activation by either epitope induces proliferation and cytokine production.

contributed to our understanding how immunological cross-reactivity can induce allergy. Birch pollen-related food allergy is now currently investigated as a disease model to elucidate whether immunological cross-reactivity can cure allergy, e.g. by cross-reactive regulatory T cells and/or cross-reactive blocking IgG4 antibodies.

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3d

HOUSE DUST MITE ALLERGENS

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KEY MESSAGES

- Many house dust mite proteins elicit IgE antibody synthesis, but for most the titres are low
- The group 1,2 and probably the newly recognized group 23 allergens are the major allergens for Dermatophagoides species
- As found for *D. pteronyssinus*, the group 4, 5, 7 and 21 allergens are quantitatively the next most important, or mid-tier, allergens
- *Blomia tropicalis* is an important source of allergens in some tropical and subtropical regions with the major specificities Blo t 5 and Blo t 21
- Mite proteases other than the group 1 allergens induce only low levels of sensitisation and very few allergens from other sources are cysteine proteases

House dust mites are the most ubiquitous source of indoor allergens inducing allergies, highly associated with asthma. They are of paramount importance in all but the few regions of the world, where they do not survive due to aridness, extreme cold or high altitude.

IgE binding studies have found that while a wide range of mite proteins can elicit antibodies most induce low or sporadically detectable titres (Table 1). Taking *D. pteronyssinus* as the exemplar, only 3 allergens bind IgE from most people at high titre, Der p 1&2 and the recently recognized Der p 23. The allergens Der p 4, 5, 7 and 21 each elicit IgE antibodies in 30-50% of mite-allergic subjects and collectively, and sometimes individually, induce titres of a magnitude considered important for the induction of disease. The group 1&2 allergens can be readily detected in dust and proprietary house dust mite extracts made from mites cultured in optimized allergen-producing conditions. The distribution of other allergens in the environment is largely unknown and frequently cannot be detected in proprietary extracts.

The evolutionary conservation of the amino-acid sequence of tropomyosin group 10 makes them a potential source of cross reactivity with allergens from a wide range of species. In most regions of the world, however, they only induce IgE in about 10% of mite-allergic subjects. There are possible exceptions mentioned in uncorroborated reports from Zimbabwe and Japan showing high titre binding, suggesting regional importance. In another example of a regional effect, aboriginals in northern Australia do not have IgE to Der p 1, 2 or 10, but instead have high titres to the amylase, Der p 4. The profile of allergens responsible for sensitisation, thus might vary from the studies conducted in urban temperate regions.

The main species that cause allergic sensitisation are *D. pteronyssinus* and *D. farinae*. The most abundant, *D. pteronyssinus* (Figure 1), is essentially the only species found in Australasia and the United Kingdom and mixed species are found elsewhere except for *D. farinae*-rich regions of central and northern Korea, northern Italy and high-latitude areas of eastern USA, where mites are found in low abundance. The allergens from these species cross react extensively so species-specificity cannot be determined by skin test. The possibility that the biochemi-

Figure 1 Stereomicroscopic view of Dermatophagoides pteronyssinus on fabric cover. Scale: mites are 0.3 mm long. Attribution: Gilles San Martin from Namur, Belgium (*By Gilles San Martin from Namur, Belgium (House dust mites Uploaded by Jacopo Werther) [CC-BY-SA-2.0], via Wikimedia Commons.*)

TABLE 1

Known important house dust mite allergens

Species	Allergen	Biochemical	Category
D. pteronyssinus	Der p 1	cysteine protease	Major
	Der p 2	ML Lipid binding	Major
	Der p 23	peritrophin	Major
	Der p 4	amylase	Mid tier
	Der p 5	unknown	Mid tier
	Der p 7	LPS/BPI family	Mid tier
	Der p 21	Der p 5-related	Mid tier
D. farinae	Der f 1	cysteine protease	Major
	Der f 2	ML Lipid binding	Major
	Other	not investigated	not investigated
B. tropicalis	Blo t 5	unknown	Major
	Blo t 21	Blo t 5-related	Major
	Blo t 7	LPS/BPI family	Mid tier

The table lists allergens shown to have IgE-binding titres expected to make significant contributions to the total anti-house dust mite titres.

LPS/BPI: lipopolysaccharide binding/bacterial permeability increasing protein

cal functions of the allergens might help promote their allergenicity has been mooted especially the cysteine protease activity of Der p 1, the lipopolysaccharide binding activity of Der p 2 and the chitin-binding of Der p 23, but this remains unproven. *Blomia tropicalis* a glycyphagoide mite found with *D. pteronyssinus* in some tropical and subtropical environments provides another source of allergens where Blo t 5 and Blo t 21 are the most important allergens and Blo t 2 is a minor specificity.

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3e

PET ALLERGENS

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KEY MESSAGES

- Exposure to pet allergens is ubiquitous in every-day life
- 10-15% of the population in affluent areas show pet allergen specific IgE
- Allergy to pets is among the most common cause of asthma and polysensitisation to several pets a risk factor for severe problematic asthma
- Allergen-specific immunotherapy for cat is efficacious, while extracts from dog and horse needs improvement

Pets of mammalian origin are common in society and kept for social, recreational or occupational reasons. In the United States alone the number of dog and cat owners is estimated to be 77.5 and 93.6 million, respectively. Pets are among the most common causes of allergy: scattered information suggests to 10-15% of the population in affluent countries. Sensitization is thought to depend on seeding of airborne particles from the pelt, saliva or urine. Upon inhalation and mucosal uptake these particles induce IgE antibodies to many identified components, Table 1, however there are many more to be identified. Allergy to pets is a risk factor for symptoms of asthma, rhinoconjunctivitis and eczema and in some areas is considered the most common cause of childhood asthma.

Figure 1 Traditionally allergens from pets are extracted from the hair. There is a growing awareness that other sources, such as saliva (Can f 2) or urine (Can f 5) may contribute critically to the IgE profile of in dog allergic patients.

To date eight cat (*Felis domesticus*), six dog (*Canis familiaris*), four horse (*Equus caballus*) and additional allergens from less common sources have been identified, Table 1. The major allergens in cat, dog and horse extracts are Fel d 1, Can f 1 and Equ c 1, with serum IgE-reactivity in allergic patients of about 95, 50 and 75%, respectively. However their proportions may vary between different geographic regions. The serum IgE profile in cat allergy is dominated by Fel d 1, whereas the profile in dog and horse is more complex. Fel d 1 is a secretoglobin glycoprotein composed of 10-20% carbohydrates, which has been suggested to increase allergenicity via mannose receptor uptake. Yet another mechanism by which Fel d 1 exerts its allergenicity is via signaling through the innate Toll-like receptors 4 and 2.

Polysensitization between pets is extensive and a risk factor for severe asthma. The most prominent group of cross-reactive allergens is the lipocalin family, including e.g. cat Fel d 4, horse Equ c 1, dog Can f 6 and rat Rat n 1. A second cross-reactive cluster are serum albumins, responsible for the pork-cat syndrome, a rare phenomenon that can lead to severe reactions. IgE to the galactose- α1,3- galactose carbohydrate

TABLE 1

Current list of characterized allergens from pets (www.allergen.org)

Animal	Allergen	Protein Family	Source	MW (kDa)	Sensitized (%)
Cat	Fel d 1	Secretoglobin	Saliva	30-38	80-95
	Fel d 2	Albumin	Dander, Sera, Urine	68	20-35
	Fel d 3	Cystatin	Dander	11	10
	Fel d 4	Lipocalin	Saliva	20	63
	Fel d 5	IgA	Saliva, Serum	28, 64	38
	Fel d 6	IgM	Saliva, Serum	28, 94	
	Fel d 7	Lipocalin	Saliva	18	38
	Fel d 8	Latherin	Saliva	24	19
Dog	Can f 1	Lipocalin	Saliva, Dander	22-25	45-55
	Can f 2	Lipocalin	Saliva, Dander	22-27	20-30
	Can f 3	Albumin	Dander, Saliva, Serum	69	15-35
	Can f 4	Lipocalin	Saliva, Dander	18	15-30
	Can f 5	Kallikrein	Urine	28	70
	Can f 6	Lipocalin	Dander	27, 29	38
Horse	Equ c 1	Lipocalin	Dander, Saliva	22	76
	Equ c 2§	Lipocalin	Dander	16	50
	Equ c 3	Albumin	Dander, Meat, Sera	65	18
	Equ c 4	Latherin	Dander, Saliva	17-19	
	Equ c 5	Latherin	Dander	17	
Guinea-pig	Cav p 1§	Lipocalin	Dander, Urine	20	70-87
	Cav p 2	Lipocalin	Dander, Tears	17-19	55-65
	Cav p 3	Lipocalin	Saliva	18-19	54
Rabbit	Ory c 1§	Lipocalin	Dander, Saliva	17-18	
	Ory c 2§	Lipocalin	Dander, Saliva	21	
	Ory c 3	Secretoglobin	Dander, Saliva	18-19	77
Rat	Rat n 1	Lipocalin	Urine	17-21	66

moiety, present in ticks bites, helminths and mammals, but not humans, has convincingly been shown to induce severe reactions after treatment with certain biopharmaceuticals and furthermore was linked to red meat food allergy.

The accuracy of pet allergy diagnostics and success of immunotherapy depends largely on the quality of the allergen source and the allergy profile of the patient. Thus, specific immunotherapy of patients with IgE sensitization to cat has proven efficacious, while specific immunotherapy of dog and horse allergy are not equally established.

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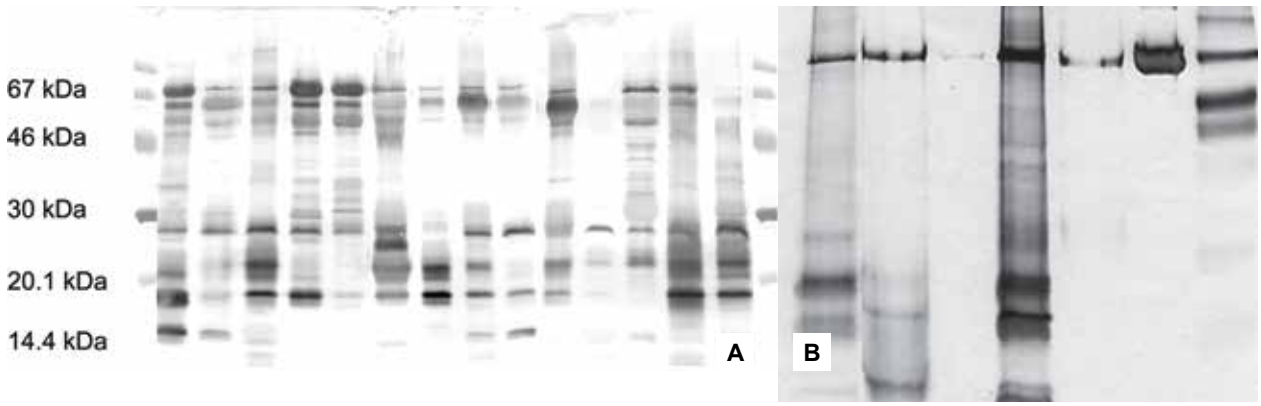

Figure 2 A) Saliva (n=14) from different dogs and breeds show variable allergen expression by IgE immunoblot using a pool of dog allergic patients. Molecular marker, left lane (*Reproduced with permission from Polovic N, Wadén K, Binnmyr J, et al. Dog saliva – an important source of dog allergens. Allergy, 2013;68:585-92, with permission from Willey Blackwell.*). B) Variability in protein content of dog dander extracts commercially available for skin prick test. Left hand lane in-house extract control, right hand side molecular markers (*Reproduced with permission from Curin M, Reininger R, Swoboda I, et al. Skin prick test extracts for dog allergy diagnosis show considerable variations regarding the content of major and minor dog allergens. Int Arch Allergy Immunol 2011;154:258–263; with permission from Karger Publishers.*)

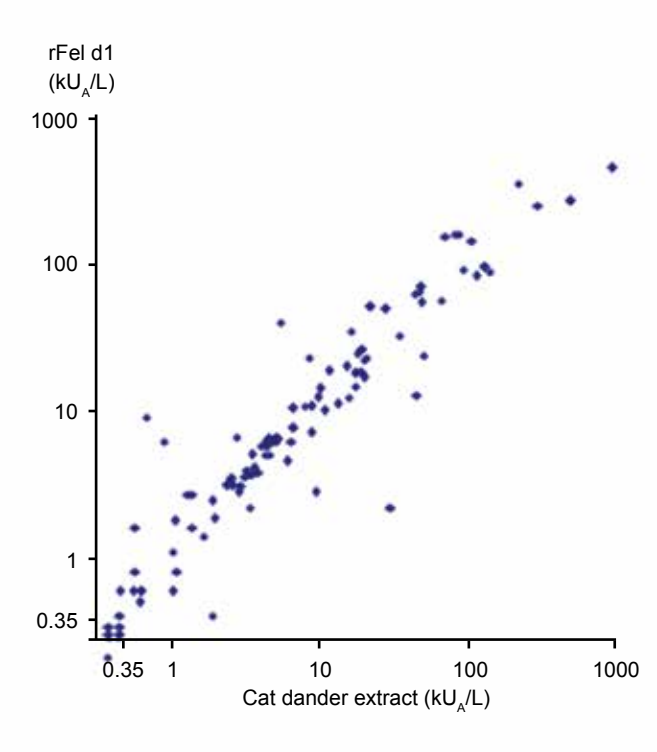

Figure 3 As opposed to dog and horse dander, one allergen, Fel d 1 (y-axis), is dominating in cat dander extracts (x-axis) as illustrated by IgE correlation analysis of 100 cat sensitized subjects using ImmunoCAP system (*Reproduced with permission from Grönlund H, Adédoyin J, Reininger R et al. Higher immunoglobulin E antibody levels to recombinant Fel d 1 in cat-allergic children with asthma compared with rhinoconjunctivitis. Clin Exp Allergy. 2008 ;38:1275-81, with permission from Willey Blackwell.*)

3f

TREE POLLEN ALLERGENS

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KEY MESSAGES

- The most clinically relevant sources of tree pollen allergens are found among *Fagales*, *Oleaceae*, and *Cupressaceae* plants, which are widely distributed worldwide
- Bet v 1-like proteins, Ole e 1- like proteins, and pectate lyases/polygalacturonases represent the major pollen allergens of *Fagales*, *Oleaceae*, and *Cupressaceae*, respectively
- Bet v 1-like allergens are responsible for allergic cross-reactions among *Fagales* pollen and various fruits and vegetables, a clinical condition referred to as oral allergy syndrome
- Ole e 1-like allergens and pectate lyases/polygalacturonases are responsible for extensive IgE cross-reactivity between *Oleaceae* and *Cupressaceae* plants, respectively

GEOGRAPHICAL DISTRIBUTION AND CLINICAL RELEVANCE

Trees belonging to the Fagales, Oleaceae, and Cupressaceae comprise the clinically most relevant sources of allergenic pollen in many regions around the world. This approach to the classification of allergenic trees according to their phylogeny provides useful guidance both for their geographical distribution and typical flowering seasons (Figure 1). Thus, Fagales trees are widely distributed within the temperate climate zone of the Northern hemisphere and predominantly flower in spring. Oleaceae trees grow in the Mediterranean areas as well as in other parts of the temperate climate zone. Their flowering season vary according to regions, ranging from early January to June. Cupressaceae plants are widely distributed in parts of Europe, Asia and Northern America, with pollination periods occurring between January and April, depending on the region. Figure 2 shows sensitization rates to representative tree pollen allergen sources in fourteen European countries.

FAGALES POLLEN ALLERGENS

Fagales pollen allergies are mainly elicited by the Bet v 1-like allergens, which belong to the family 10 of plant pathogenesis-related proteins. Besides cross-reactivity between Fagales trees, Bet v 1 sensitization often leads to allergic reactions to various fruits and vegetables due to homologous proteins found in certain plant families, including Rosaceae, Apiacea, and Fabaceae (Figure 3). Furthermore, pan-allergens belonging to the families of calcium-binding proteins and profilin contribute to the extensive food and pollen cross-reactive patterns observed among Fagales-sensitized patients.

OLEACEAE POLLEN ALLERGENS

Ole e 1-like glycoproteins represent the major allergen of allergenic Oleaceae trees, including olive, ash, and privet (Table 1). It has been shown that exposure to high loads of olive pollen can lead to increased sensitization rates to minor allergens (lipid-transfer proteins, 1,3-beta-glucanase) and correlates with more severe allergic symptoms, including asthma.

CUPRESSACEAE POLLEN ALLERGENS

The major pollen allergens from Cupressaceae trees (e.g. cypress, mountain cedar, Japanese cedar) belong to the family of pectate

Figure 1 Word maps showing the distribution of trees causing respiratory allergic reactions. Representative members of the Fagales family (Betula and Quercus), the Oleaceae family (Olea and Fraxinus), and the Cupressaceae family (Cryptomeria and Juniperus) are depicted in the maps as density of registered data (increasing density from yellow to orange) within the Global Biodiversity Information Facility (www.gbif.org), a free and open access data infrastructure funded by governments.

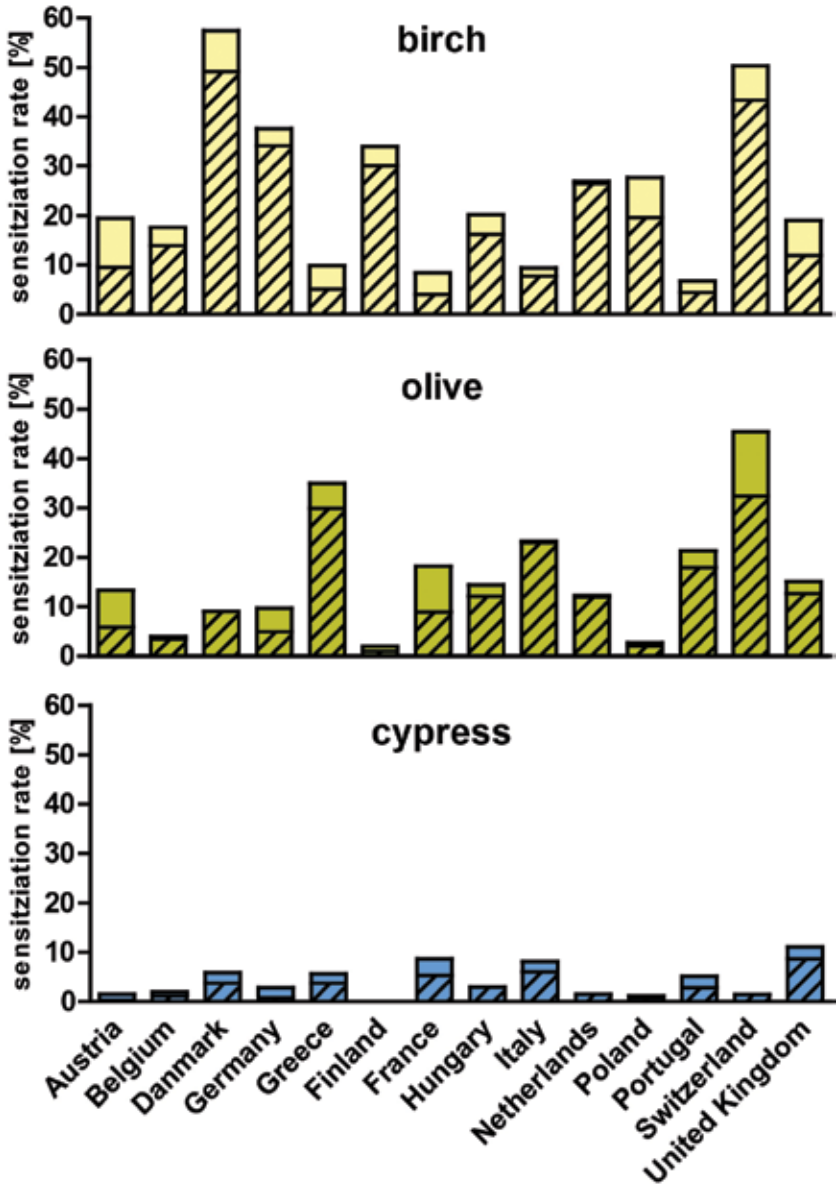

Figure 2 Sensitization (colored) and clinically relevant sensitization rates (striped) to tree pollen allergens from the GA2LEN skin test study II. Patients (n=3034) referred to allergy clinics in 14 European countries were diagnosed using skin prick test extracts of birch, olive and cypress. In Northern and central European countries, a high prevalence to birch pollen was observed while reactivity to cypress was generally low. Sensitization to olive was most abundant in Switzerland and Greece suggesting an involvement of cross-reactive ash-tree pollen. The majority of sensitized patients (66%-75%) displayed clinical symptoms to the allergen elicitor. (*Reproduced with permission from Burbach GJ, Heinzerling LM, Edenharter G, et al. GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe.Allergy 2009,64:1507-1515, with permission from Willey Blackwell.*)

lyases and polygalacturonases. Natural purified Cupressaceae allergens display extensive IgE cross-reactivity, which is partly due to the presence of cross-reactive carbohydrate determinants. In addition, the overlap of flowering period with winter flu seasons complicates the clinical diagnosis of Cupressacea pollen allergies.

CONCLUSION

The major allergens of Fagales, Oleaceae, and Cupressaceae belong to distinct families of proteins, and thus represent ideal tools for molecule-based diagnosis and therapy of tree pollen allergies.

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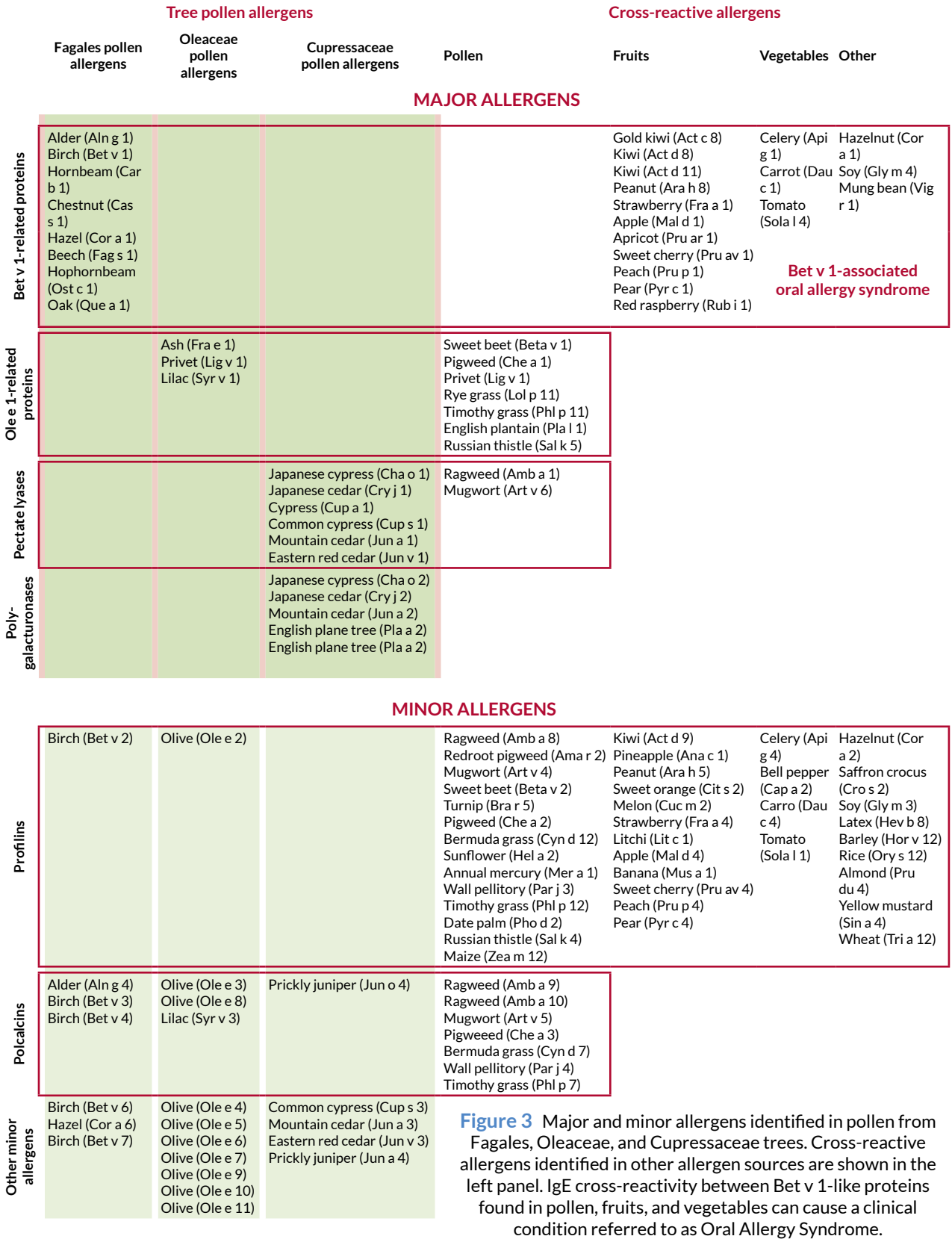

Figure 3 Major and minor allergens identified in pollen from Fagales, Oleaceae, and Cupressaceae trees. Cross-reactive allergens identified in other allergen sources are shown in the left panel. IgE cross-reactivity between Bet v 1-like proteins found in pollen, fruits, and vegetables can cause a clinical condition referred to as Oral Allergy Syndrome.

3g GRASS POLLEN ALLERGENS

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KEY MESSAGES

- Pollens from diverse grass plants are main contributors to seasonal inhalant allergies worldwide
- Grass group 1 and 5 allergens represent highly cross-reactive and potent major allergens, group 5 present only in temperate climate grasses (Pooideae)
- Depending on climate and region, global sensitization rates to grass pollen vary between 1% to 30% of the general population
- Strong evidence supports specific immunotherapy with grass pollen extracts

BOTANICAL RELATIONSHIP

Grasses are ubiquitous plants in most parts of the world. The grass family (*Poaceae*) includes >600 genera and >11,000 recognized species with a wide distribution. Over 95% of allergy-relevant grass species belong to three subfamilies; *Pooideae*, *Chloridoideae* and *Panicoideae* (Figure 1 and 2).

GLOBAL DISTRIBUTION

Depending on climate and geography, grass pollens represent major contributors of airborne allergens during spring as well as summer. They grow on all continents and represent 25% to 35% of the earth´s vegetation. *Pooideae* dominate temperate climate zones; *Chlorodoideae* cover the North American, African and Australian continents and *Panicoideae* grow in tropical and subtropical environments of Asia, Australia, Africa and South America (Figure 3).

ALLERGENS OF GRASS POLLEN

Grass pollen allergens are grouped according to their protein structure and function (Table 1). They are named according to the official nomenclature (www.allergen.org), i.e.: Phl p 1 = grass group 1 allergen from *Phleum pratense* (timothy grass). Ten designated groups consist of major (>50% sensitization rate, SR) and minor allergens (<50% SR). Due to their abundance and potency, grass group 1 and 5 allergens are considered immunodominant major *Pooideae* pollen allergens (Figure 4). While group 5 allergens are restricted to the *Pooideae* subfamily, group 1 allergens are present throughout the subfamilies of *Poaceae*. In contrast, pan-allergens profilin (group 12) and polcalcin (group 7) contribute to ubiquitous cross-reactivity between grass, tree and weed pollen in 10 – 15% of grass pollen sensitized subjects. Present concepts of homologous allergen groups, are based on similar biochemical composition, homology and immune cross-reactivity reflecting in most cases their close taxonomic relationship and have been adopted by the European Medicines Agency (EMA).

CLINICAL ALLERGY BASED ON SENSITIZATIONS

Sensitizations to grass pollen allergens, indicated by grass pollen allergen (extract) positive skin test or specific IgE, reflect regional plant distribution and pollen exposure. Population based sensitization rates are mainly available for Europe and the US and vary considerably between and within countries (Figure 5). Grass pollen allergy is a global problem (Figure 5c). At least half of grass pollen allergen sensitized subjects will suffer from symptoms of allergic rhinoconjunctivitis and/or bronchial asthma, particularly during the warm seasons in moderate climate regions.

Figure 1 Pictures of different grass species and their pollen : a - Timothy grass (*Phleum pratense*), subfamily Pooideae; b-Bermuda grass (*Cynodon dactylon*), subfamily Chloridoideae; c - Bahia grass (*Paspalum notatum*), subfamily Panicoideae.

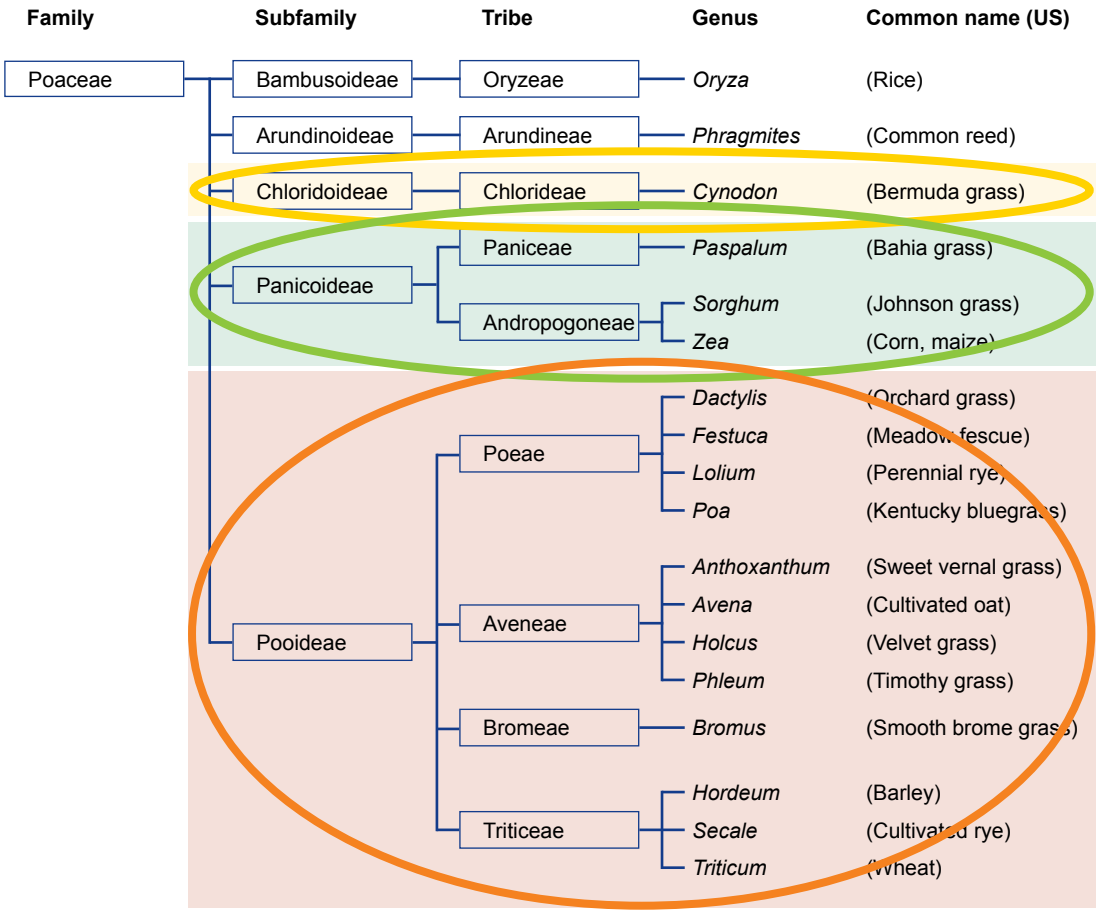

Figure 2 Taxonomy of grasses (important subfamilies within colored boxes). Overlapping circles (colored lines) indicate partial cross-reactivity between neighboring subfamilies (modified from (2), (4) and (10)).

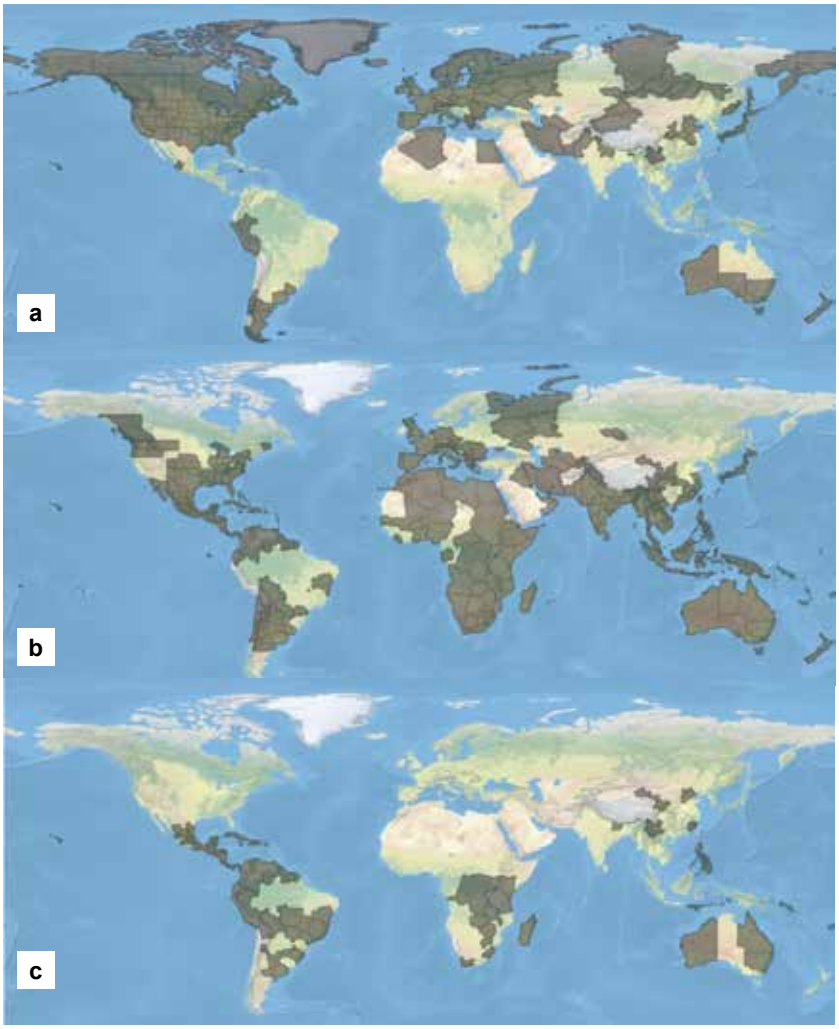

Figure 3 Global distribution of selected grass species (10): a- Timothy grass (*Phleum pratense*), subfamily Pooideae; b-Bermuda grass (*Cynodon dactylon*), subfamily Chloridoideae; c-Bahia grass (*Paspalum notatum*), subfamily Panicoideae.

DIAGNOSIS AND TREATMENT

Positive skin prick tests and elevated specific serum IgE to grass pollen preparations indicate allergic sensitizations, being clinically relevant only in case of corresponding symptoms. Measuring IgE to major allergens (i.e. Phl p 1 and 5) increases analytical specificity for temperate grass pollen allergy, particularly in case of sensitizations to cross-reactive pollen-panallergens. Specific immunotherapy is most successfully applied for at least three years by subcutaneous injections or sublingual home use of droplets or tablets with monopreparations of one grass species, but also grass mixes (mainly Pooideae), with or without adjuvants.

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TABLE 1

Grass pollen allergen groups

Allergen group	Biochemical function	Molecular-weight [kDa]	Member in *Phleum pratense*	Features	IgE reactivity
1	β-expansin	27 - 35	Phl p 1	Glycoprotein, major grass pollen allergen, produced by every grass species	>90% 85-99%
2	Unknown	11	Phl p 2	highly homologous to group 3 and C-terminal portion of group 1 allergens	35 - 50% 40-60 %
3	Unknown	11 - 14	Phl p 3	highly homologous to group 2 and C-terminal portion of group 1 allergens	35 - 70% 57-67 %
4	Oxidoreduc-tase	50 - 60	Phl p 4	Glycoprotein, Berberine bridge enzyme family member, plant pathogen response system	50 - 75% 45 - 88%
5	Unknown	27 - 35	Phl p 5	found in Pooideae grass species, associated with submicronic cytoplasmic starch particles	65 - 85% 50 - 88 %
6	Unknown	12 - 13	Phl p 6	homologous to internal group 5 sequences, only in *Anthoxanthum odoratum*, *Phleum pratense* and *Poa pratensis*	60 - 70% 45 - 70%
7	Polcalcin, Ca^{++}-binding protein	8 - 12	Phl p 7	Panallergen, dimer assembly in grass pollen, broad pollen-related crossreactivity	5 - 35% 2 - 12%
11	Ole e 1-related protein	16 - 20	Phl p 11	Glycoprotein, similar structure to pollen allergens from olive tree pollen (Ole e 1) and lamb´s quarter (Che a 1)	18 - 56%
12	Profilin	13 - 14	Phl p 12	Panallergen, highly conserved, broad pollen and plant food-related crossreactivity	10 - 40% 9 - 32%
13	Polygalacturo-nase	45 - 60	Phl p 13	Glycoprotein, susceptible to protease degradation	30 - 40% 36 - 56 %

Modified from (1). Due to their taxonomic and biochemical relationship, many grasses contain similar allergens grouped according to shared amino acid sequences. Specific allergens from timothy grass (Phleum pratense, see middle column) are given as examples of the listed grass allergen groups.

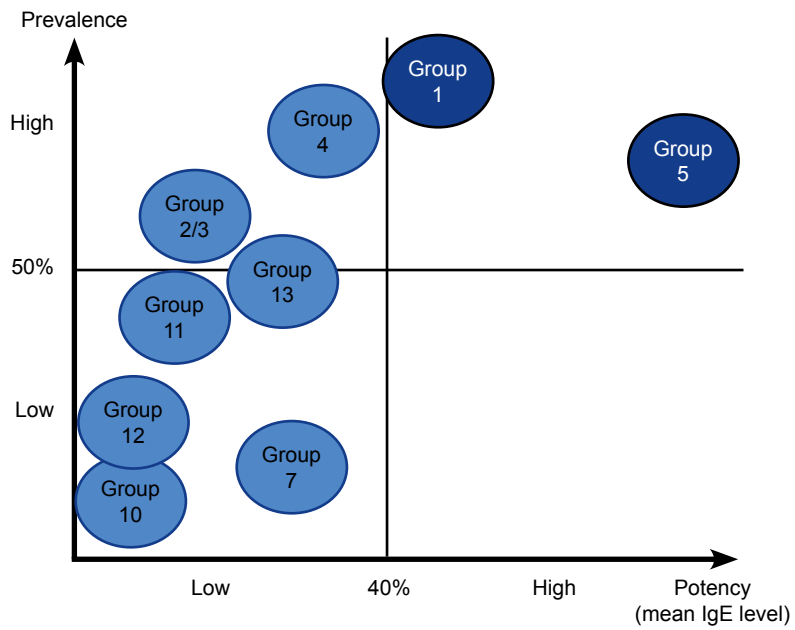

Figure 4 Involvement of grass pollen allergens in patient sensitization (3).

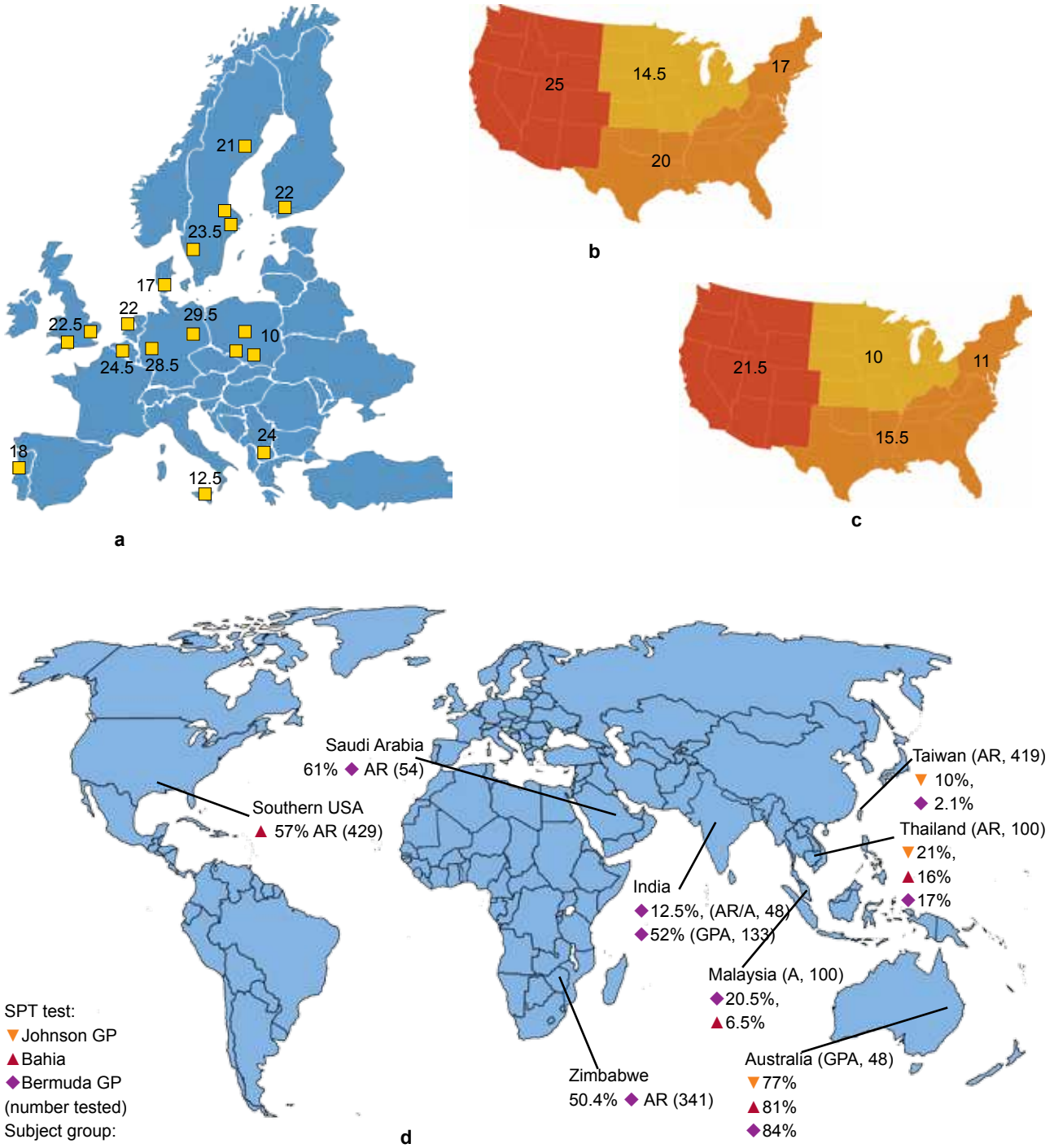

Figure 5 Sensitization rates to grass pollen (*Pooideae*) in Europe (a: modified from (7)), to Ryegrass (b) and Bermuda grass (c) in the US (b and c: modified from (8)) and to Johnson, Bahia and Bermuda grass pollen elsewhere (d: limited information, modified from (9)).

3h

WEED POLLEN ALLERGENS

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KEY MESSAGES

- The major weeds families inducing allergic rhinitis are the Amaranthaceae, the Asteraceae and the Urticaceae
- Cross-reactivity between family members is frequent
- In most temperate regions the weeds pollen season is August and September, but climate change can be associated with a lengthening of the pollination period

Weeds can be defined as unwanted plants; as such, they may be very variable in form. While many are herbaceous, some have greater or lesser woody stocks, for example the sagebrushes, *Artemisia tridentata* and *A. frigida*. Some are prostrate and hug the ground, while others, such as giant ragweed, *Ambrosia trifida*, may be over 3 meters high. Herbaceous varieties may be annuals or perennials. Weeds found in numerous botanical families can be inducers of allergic rhinitis and asthma, but a few families stand out with the majority of aeroallergen sources.

Amaranthaceae contains the pigweeds (*Amaranthus*), saltbushes (*Atriplex*), and tumbleweeds (*Salsola*, *Kochia*, *Bassia*) as well as other chenopod weeds (*Chenopodium*). The latter three groups were earlier placed in a separate family, Chenopodiaceae. More recent systematics has, however, redefined this group as a subfamily of Amaranthaceae. The major tumbleweeds of the North American Great Plains are Russian thistle (*Salsola kali*) and burning bush (*Kochia scoparia*): both are introduced plants. Other species of *Salsola* and *Bassia* are common throughout the Middle East. The *Atriplex* saltbushes are common in arid floristic zones. Redroot pigweed (*A. retroflexus*) is a ubiquitous cosmopolitan weed, found throughout temperate regions of the globe. Allergenic cross-reactivity is very strong amongst the *Atriplex* weeds, and likewise between the *Amaranthus* species examined; cross-reactivity between other chenopod weeds is present but more variable.

Asteraceae (previously known as Compositae) is the largest family of flowering plants (Angiospermae), and contains several notorious inducers of pollinosis. The genus *Ambrosia* contains all the ragweeds, including several reclassified from the discarded genus *Franseria*. The four major ragweed (*Artemisia*) species are giant (*A. trifida*) (Figure 1), short (*A. artemisiifolia*) (Figure 2), western (*A. psilostachya*), and false (*A. acanthicarpa*). These are all North American natives, but most of them have been introduced into Europe, and have rapidly expanded across the Balkans, Ukraine, and into Poland. In most temperate regions the pollen season is August and September. Cross-allergenicity is strong amongst the major ragweed species. Other important members of Asteraceae are in the genus *Artemisia*, the sages. There are about a dozen species found in the United States. The most prevalent in eastern U.S. and Europe is mugwort (*A. vulgaris*). Fringed sagebrush (*A. frigida*) is a common groundcover in the Siberian steppes. Cross-reactivity is very strong between *Artemisia* species.

Urticaceae includes two members of significance: pellitory (*Parietaria*) (figure 3) and nettle (*Urtica*). Pellitory is a major seasonal aeroallergen of the Mediterranean Basin. Climate change is associat-

Figure 1 a - Giant sagebrush (*Artemisia*); b - short ragweed; c- pellitory (*Parietaria*).

ed with a lengthening of its pollen season to about ten months.

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3i

FOOD ALLERGENS

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KEY MESSAGES

- Differences in sensitization to food allergens across different geographic regions have been particularly observed for plant food allergens
- 65% of plant food allergens are part of four protein families/superfamilies: the prolamin, cupin, Bet v 1 and profilin family
- In Europe, the prevalence of IgE to foods significantly correlates with the prevalence of sensitization to birch-pollen-associated allergens Bet v 1 and Bet v 2
- Food allergic patients from Mediterranean countries show a higher sensitization rate to profilin and non-specific lipid transfer proteins compared to Central, Western or Eastern Europe

Depending on the route of sensitization, immediate-type food hypersensitivities are either a result of reactivity to food allergens through the gastrointestinal tract (class I allergens) or the result of secondary sensitization to cross-reactive food allergens mainly due to primary sensitization to homologous pollen allergens via the respiratory tract (class II allergens, Figure 1). Class I allergens are often resistant to heat, degradation and digestion. Class II allergens are mainly labile and easily degradable. According to these characteristics the clinical manifestation is influenced by the type of allergens to which an individual is sensitized. The class I allergens have a higher potential to induce severe reactions compared to the easily degradable class II food allergens, which induce often symptoms restricted to the oral cavity. Due to such reasons, great efforts have been made in the last few years to identify and characterize individual food allergen molecules in the most prevalent allergenic foods (http://www.allergen.org/; http://www.allergome.org/; http://www.meduniwien.ac.at/allergens/allfam/) and to compare sensitization patterns between different geographic regions.

More than 65% of plant food allergens are members of just four protein families/superfamilies: the prolamin, cupin, Bet v 1 and profilin family (Table 1). Animal derived food allergens mainly belong to three protein families: the tropomyosins, parvalbumins and caseins.

At school age, adolescence and adulthood cross-reactive food allergy is dominating. According to new epidemiologic data sensitization to the respective food allergens is heavily dependent on the exposure and sensitization to inhalant allergens. In a recent study including adult participants from eight European centres the prevalence of IgE to foods ranged from 6.6% (Iceland) to 23.6% (Switzerland) and was significantly correlated with the prevalence of sensitization to birch-pollen-associated allergens Bet v 1 and Bet v 2 (profilin), whereas IgE sensitization to non-pollen-related plant allergens were more evenly distributed. These results confirmed the findings from studies evaluating the sensitisation pattern to food allergens across Europe. Sensitization rates to the Bet v 1 homologous proteins in apple (Mal d 1), kiwi (Act d 8), carrot (Dau c 1) or hazelnut (Cor a 1) were significantly higher in countries with high birch pollen exposure such the Netherlands, Austria, Northern Italy, Switzerland and Denmark com-

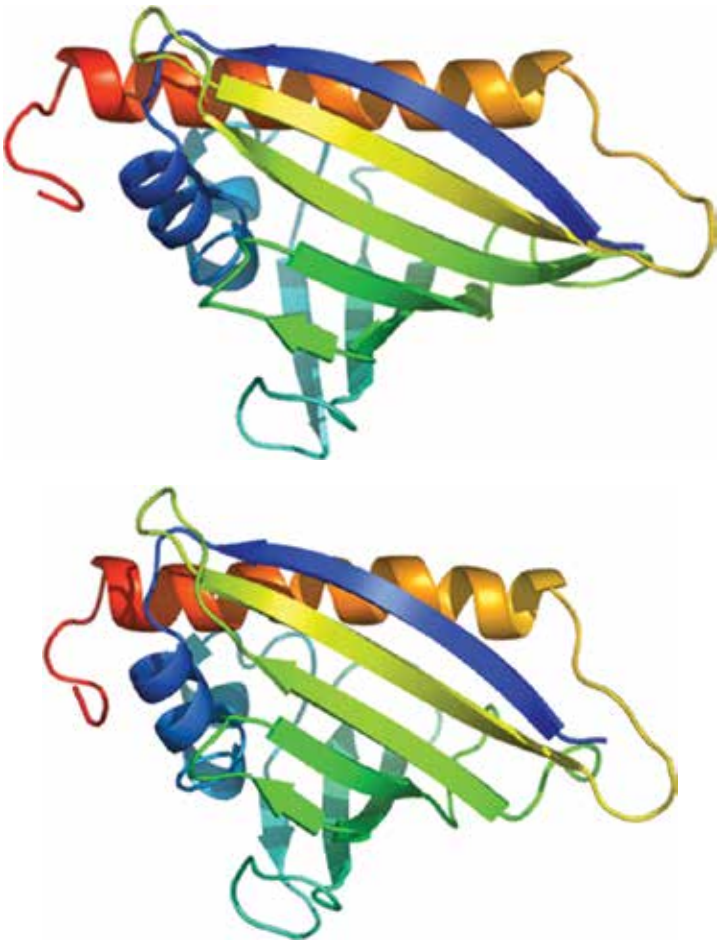

Figure 1 Homology between the major birch pollen allergen Bet v 1 and homologous food protein. High structural homology between the major birch pollen allergen Bet v 1 (top) and homologous food protein (here as an example the cherry allergen Pru av 1, bottom) explains the phenomenon of cross-sensitization between birch pollen and plant foods and the high prevalence of sensitization to foods in birch pollen exposed regions of Europe.

TABLE 1

Most important protein families for plant food allergies

Protein family	Prolamin		Cupin		Profilin	Bet v 1	Thaumatin-like protein
Biochemical structure	2S albumin	nsLTP	7S-globulin vicilin	11S-globulin legumin			
function	storage protein	plant defense	storage protein	storage protein	actin binding	pathogen resistance PR-10	pathogen resistance PR-5
examples of foods	peanut, soy, tree nuts, sesame, mustard	Rosaceae fruits, nuts, seeds, vegetables	peanut, soy, pea, lentil, nuts, sesame	peanut, soy, nuts	all plant foods	Rosaceae fruits, nuts, legumes, vegetables	cherry, apple, peach, tomato, orange, grape, kiwi, bell pepper

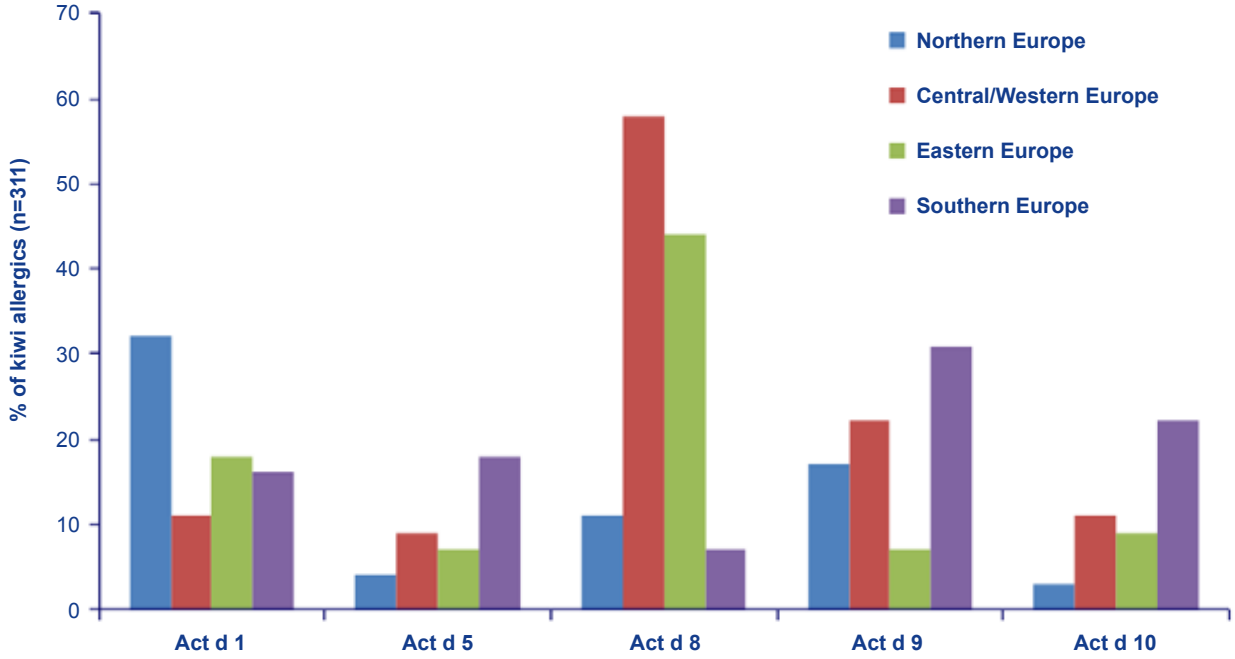

Figure 2 Sensitization pattern to kiwi allergens. Sensitization pattern to kiwi allergens Act d 1 (Actinidin), Act d 5 (Kiwellin), Act d 8 (Bet v 1 homologous protein), Act d 9 (Profilin) and Act d 10 (non-specific LTP) in four European regions (northern: Iceland; central/western: France, northern Italy, Switzerland, The Netherlands, United Kingdom; eastern: Bulgaria, Poland, Czech Republic, Lithuania, southern: Spain, Greece). Patients from Iceland were mainly sensitized to Act d 1 (32%), those from western/central and eastern Europe to Act d 8 (58% and 44%, respectively), and those from southern Europe to Act d 9 (profilin, 31%) and Act d 10 (non-specific LTP, 22%) (Le et al., J Allergy Clin Immunol 2013).

pared to that observed in Mediterranean countries such as Spain or Greece (Figure 2: sensitization pattern to kiwifruit allergens across Europe). Spanish and Greek patients, however, showed a higher sensitization rate to profilin and non-specific Lipid transfer protein (LTP). A similar association of sensitisation to pollen from the Betulaceae family, particular alder, and the development of fruit allergy was observed in Japan. Sensitization to food LTP is highly prevalent in Mediterranean countries and associated with a higher rate of systemic reactions. Also in China sensitization to peach LTP, Pru p 3, was associated with a high rate of systemic reactions.

Differences in the sensitization pattern were also demonstrated for children with peanut allergy from three different geographic regions. Spanish patients were mainly sensitised to non-specific LTP (Ara h 9), Swedish patients to the Bet v 1 homologous allergen Ara h 8 and US patients to the storage proteins in peanut Ara h 1, Ara h 2 and Ara h 3.

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3j VENOM ALLERGENS

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KEY MESSAGES

- 12 molecular allergens of honey bee venom, and five of Vespula venom are known and have been sequenced
- Use of molecular allergens has improved testing of venom-specific IgE antibodies
- Further research on the clinical role of individual molecular insect venom allergens is needed
- Allergen components of the venoms should be available for routine testing

INSECTS

For allergic sting reactions, mainly social *Aculeatae* are important elicitors. Social insects have developed a division of labour with sterile females forming a working class. Female workers have a stinger by which venom is injected during a sting into the skin. Within the *Aculeatae*, *Vespidae* (vespids), *Apidae* (bees), and *Formidaceae* (ants) are social insects (Figures 1 and 2). *Vespidae* are divided into the subfamilies *Polistinae* and *Vespinae*. The latter contains three genera: Vespula, Dolichovespula and Vespa.

INSECT VENOMS

Insect venoms contain a complex mixture of toxic proteins and peptides, of which some may induce IgE-mediated sensitisation. Today, 12 molecular allergens of honey bee venom, and 5 of Vespula venom are known and have been sequenced (Table 1). For some of these allergens, isoforms have been detected.

Major allergens are characterized by the fact that there is corresponding specific IgE-antibodies (sIgE) in the blood of the majority of allergic patients. Major allergens are probably more important than minor allergens in terms of eliciting an allergic reaction. Minor allergens may also induce sIgE, however, this occurs in a small percentage of venom allergic patients.

Phospholipase A2, hyaluronidase, and acid phosphatase are the major bee venom allergens. Major allergens of *Vespula* venom are Phospholipase A1, Hyaluronidase, and Antigen 5. Some allergens of *Vespula* and bee venom share minor to moderate sequence identity and show a corresponding cross-reactivity. However, the closer is the taxonomic relationship of insects the greater is the overlap of biochemical structures of molecular venom allergens. Honey bee venom allergens show more cross-reactivity with bumble bee allergens compared to allergens of the venoms from *Vespula*

Figure 1 a - Apidae (bee); b- Vespidae (vespids).

TABLE 1

Most important protein families for plant food allergies			
Allergen	**Name / Function**	**Molecular weight (KDa)**	**Percent of dry weight**
Honey bee venom allergens			
Api m 1	Phospholipase A2*	16	12
Api m 2	Hyaluronidase*	39	2
Api m 3	Acid phosphatase	43	1-2
Api m 4	Melittin*	3	50
Api m 5	Dipeptidylpeptidase IV	100	<1
Api m 6		8	1-2
Api m 7	CUB serine protease	39	?
Api m 8	Carboxylesterase	70	?
Api m 9	Serine carboxypeptidase	60	?
Api m 10	Icarapin variant 2, carbohydrate-rich protein	50-	<1
Api m 11	Major royal jelly protein	50 (deglycosylated form)	?
Api m 12	Vitellogenin	200	?
Vespula venom allergens			
Ves v 1	Phospholipase A1*	34	6-14
Ves v 2	Hyaluronidase*	28	1-3
Ves v 3	Dipeptidylpeptidase IV	100	?
Ves v 5	Antigen 5*	23	5-10
Ves v 6	Vitellogenin	200	?

(IUIS Allergen Nomenclature Sub-Committee. www.allergen.org). Major allergens are indicated by an asterix (*)

species. Venom allergens from *Polistinae* or *Dolichovespula* are more related to *Vespula* venoms.

IN-VITRO DIAGNOSTICS OF VENOM SENSITIZATION

Demonstration of venom-specific sensitization is essential for diagnosing an insect venom allergy and is also a prerequisite to select the proper venom for immunotherapy. To identify venom-specific IgE in human blood, insect venoms are in use since the seventies. In the late eighties, purified allergens were produced. Today, one recombinant allergen component of honey bee venom (Api m 1) and two of Vespula venom (Ves v 1 and 5) are available for routine diagnostics. It is assumed that in the near future more molecular compounds will be available to identify venom sIgE.

In contrast to certain food allergies, where the sensitization patterns were found to be associated with mild or severe allergic reactions and can be used for risk assessment, for venom allergy, the clinical relevance of a certain pattern of venom sIgE remains unclear.

Testing sIgE to single venom allergens is of major importance for improving sensitivity and specificity of in-vitro diagnostics. Using recombinant allergens improved the value of assays testing sIgE to the whole venom.

Another problem for the diagnosis of insect venom allergy is the double positivity although presumably the patient only suffers from one allergy. Double positivity may be due to true double allergy, to cross reactivity between allergen compounds of honey bee and Vespula venoms, and to sensitization to widespread cross-reactive carbohydrate determinants (CCD), which are present in many allergen sources from plants and animals. The latter, however, usually do not act as allergens. Allergen compounds, which are free from CCD improve the specificity of in vitro testing.

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3k

EMERGING ALLERGENS

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KEY MESSAGES

- Only a minority of known proteins exert an allergenic activity
- Allergen panels contribute to improve in vitro diagnosis of allergy
- While some allergens rather induce mild symptoms, others are known to be linked with severe symptoms (marker allergens)
- Depending on environmental exposure and dietary habits IgE recognition patterns may vary in different patients groups

In the recent past, great efforts have been undertaken to characterise allergens. This in turn has revolutionized *in vitro* diagnosis, by determining the range of cross reactivities and establishing allergen panels. Of special interest is the identification of marker allergens: allergens that tend to induce rather severe symptoms versus allergens that rather account for mild symptoms.

It is only a minority of proteins that exert allergenic activity. To date allergens can be assigned to 2% of all known protein families. According to allergen databases, the dominating protein families among animal-derived food allergens are tropomyosins, parvalbumins and caseins. Similarly, prolamins, cupins and PR10 proteins are the 3 most important plant protein families (Table 1).

ANIMAL-DERIVED FOOD ALLERGENS

Tropomyosins are highly conserved eukaryotic proteins with a typical coiled-coil structure that are necessary for regulating muscle contraction. So far, allergenic tropomyosins have been identified from e-vertebrates, highly cross-reactive among crustaceans and mollusks, as well as inhalant allergens from mites and cockroaches.

Parvalbumins share an EF-hand domain binding Ca^{2+} and thus are involved in signaling pathways or Ca^{2+} transport. These major food allergens were identified from fish and amphibians, but not from higher vertebrates.

Caseins are a major heterogenous protein fraction in mammalian milk displaying a random-coiled structure. They function as Ca^{2+} binders and allergenic caseins and are highly cross-reactive among mammalian species.

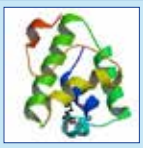
So far sensitization to carbohydrates has been regarded as of low clinical importance in allergic diseases. However, recently, allergic reactions to alpha-gal epitopes were observed in meat allergy. Previous administration of monoclonal antibody doses induced the sensitization event. This highlights that alternative exposures have to be considered if new and unexpected cases of allergies occur.

PLANT-DERIVED FOOD ALLERGENS

The **non-specific lipid transfer proteins** (LTP) and the **2S albumins** belong to the **prolamin superfamily**. Both types of proteins display a rigid tertiary structure and are resistant to enzymatic and thermal treatment. Non-specific-LTPs are involved in plant defense, and are relevant allergens in various fruits, nuts and pollens. 2S albumins are seed storage proteins and together with the proteins from the **cupin superfamily** they represent important allergens in seeds and nuts, usually evoking severe symptoms in patients. The **PR10 proteins**, involved in plant defense, are present in pollen as

TABLE 1

Overview of 3 most important plant and animal food allergen protein families

Protein superfamily	Protein family	Biological function	Molecular mass (kDa)	Allergens known from	Structure
Animal food allergens					
	Tropomyosin	Muscle contraction	36-38	Crustaceans, molluscs	 PDB: 1C1G
	Parvalbumin	Ca^{2+} binding	12	Fish, amphibians	 PDB:1B8R
	Casein	Ca^{2+} binding	20-30	Mammalian milk	Not available
Plant food allergens					
Prolamin superfamily	**2S Albumin**	Seed storage	15-17	Peanut, tree nuts, seeds	 PDB: 1PNB
	ns-LTP	Plant defense	7-9	Plant food	 PDB: 2B5S
Cupin superfamily	**7/8S globulin**	Seed storage	150-190	Legumes, nuts, seeds	 PDB: 3SMH
	11S globulin	Seed storage	60	Peanut, tree nuts, seeds	 PDB:3FZ3
	PR10	Plant defense	17	Plant food	 PDB: 2BKO

(ns-LTP – non-specific Lipid transfer protein; PR10 – pathogenesis related protein family 10; structures retrieved from pdb)

well as in plant food, usually evoking mild oral symptoms. Eventually, they can induce severe symptoms as in soy allergy.

In conclusion, a number of allergens are now available for component-resolved in vitro diagnosis. Analysis of their physicochemical features, especially their 3D structure contributes to our understanding of protein stability, range of cross reactivity and changes in allergenicity during thermal or enzymatic treatment.

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31 POLLEN ALLERGENS AND GEOGRAPHICAL FACTORS

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Allergies to pollen are the most frequent type 1 allergies, surpassing the prevalence of allergies to house dust mite. Their prevalence have been increasing since decades and an end is not in sight.

Pollen is a natural product and shows a large geographical and climatic variability. Indeed, natural variability is so large that a simple prediction of pollen load depending on the year long experience is not possible. This has led to the implementation of pollen monitoring networks.

KEY MESSAGES

- Pollen exposure varies between geographical regions
- The same amount of olive pollen releases 12-fold variable amounts of Ole e 1, 10-fold differences in Bet v 1 is documented for birch pollen, while Phl p 5 from grass pollen can show even higher variations
- Pollen allergen release potency is not geographically fixed and changes between years
- Pollen allergen release potency is determined in the week before pollination by two simultaneous competing ripening processes: anther development and individual pollen ripening

GEOGRAPHIC FACTORS AND POLLEN EXPOSURE

Few pollen monitoring networks exist worldwide (Figure 1). In addition, rotorod samplers are used in USA, while Hirst-type pollen traps are frequent in Europe making quantitative comparison between continents challenging.

However, similar results emerge: pollen exposure varies substantially. For Europe, according to a 20-year average, birch pollen is the dominant pollen with 2-times higher counts than grass pollen in almost all reported locations. Between locations, a 10-fold difference of pollen load was noted (Figure 2).

Climate change is reported to influence pollen season for the starting date and for the intensity for early blooming species. The natural yearly variability in pollen exposure is large, making the effect of climate change difficult to predict. An elongation of the birch pollen season was reported only in a few random places. Pollen exposure is mostly dependent on short-term local weather, making on the spot monitoring an essential instrument in determining exposure.

GEOGRAPHICAL FACTORS AND POLLEN POTENCY

Pollens are natural products and like wine and strawberries their "quality" depends on the climatic conditions at source, which varies with the geographical location. The amount of allergen released per pollen is variable between years, locations and even days. In a EU-wide project (www.hialine.eu) the allergen release potency for olive, birch and grass pollen was analyzed with standardized methods. Across Europe, pollen potency varied 12-fold for olive pollen, 10-fold for birch pollen and even more for grass pollen. Also, potency of pollen from olive and birch depended on the origin of emission as potency is determined by weather at the place of emission, not at the place of measuring the pollen. Within Germany, a constant 3-fold gradient of birch pollen potency is observed, with

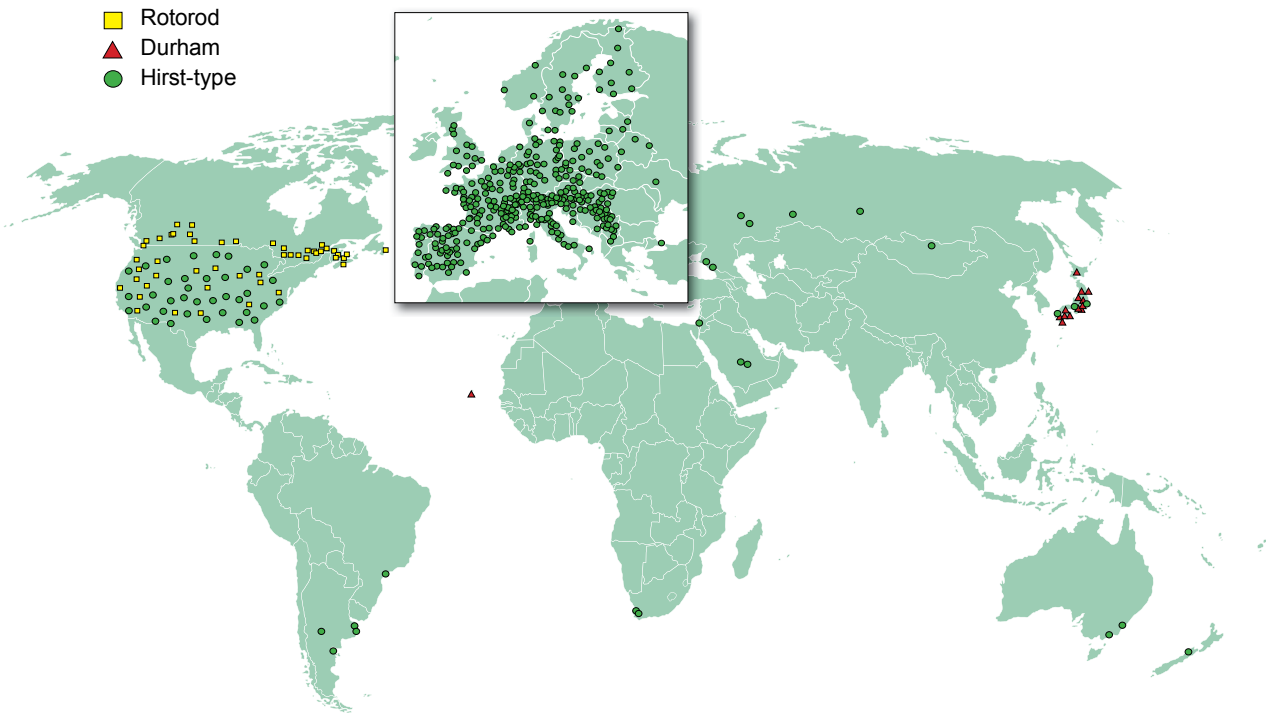

Figure 1 Pollen monitoring networks across the world. Current pollen monitoring sites running for more than 6 years. Three different types of pollen counters are in use worldwide: Rotorod, Durham and Hirst-type traps. This makes pollen counts difficult to compare. Data from Europe were provided by U. Berger, European Aerobiology Network (EAN), Medical University Vienna, from USA by Jerome Schultz (AAAAI), from Russia by E. Severova, from Japan by R. Kishikawa, from South Africa by D. Byrman, from Israel by A. Eshel, from Saudi Arabia by H. Syed, from Azores by Rui Brandao, from Canada by F. Coates and from Australia by Janet Davies. For some countries data was not available.

southern pollen being more potent that northern pollen. In the same line, olive pollen from Spain released 5 times more Ole e 1 than Portugese olive pollen.

The difference in pollen potency could be due to two competing ripening processes: allergen expression in pollen increases from zero in the week before pollination to high numbers upon pollination (ripening of Bet v 1). Concomitantly the anthers ripen too, and will release pollen when they are ripe and weather is suitable. Thus, bad weather can result in late opening of anthers and consequently long ripening periods for the allergen, resulting in more potent pollen.

CONCLUSION

All investigated aeroallergens:pollen from birch, olive and grass, but also from cat, dog and horse vary at least 10-fold in allergen release within the same species. We expect the same for other sources.

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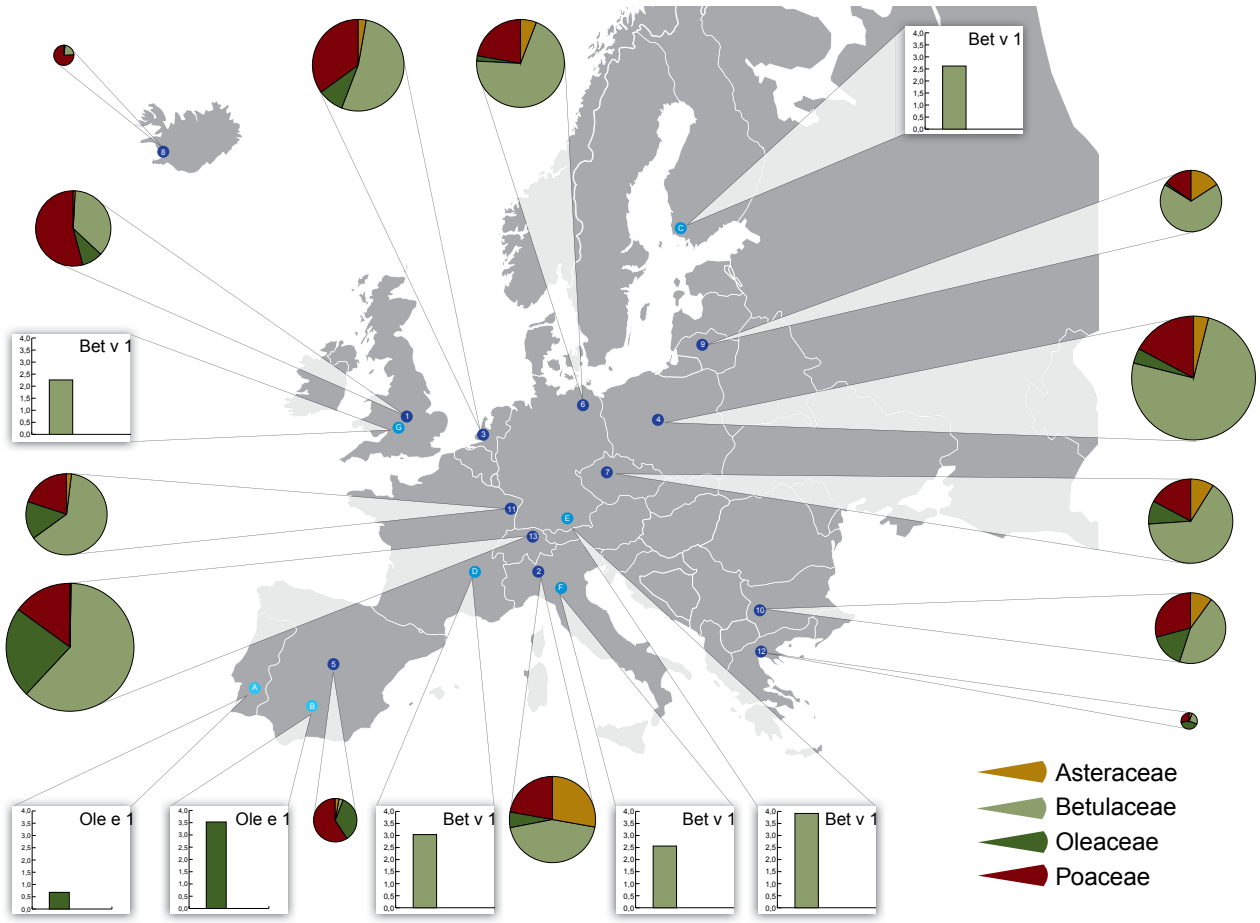

Figure 2 Pollen distribution and pollen potency across Europe. Size of the circles represents quantitative differences in the pollen index, colors represent different pollen species (families). Bar graphs represent the amount of allergen released per pollen (potency) for the indicated locations.

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4 THE UNDERLYING MECHANISMS IN ALLERGY

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KEY MESSAGES

- The early development of memory T and B cell responses and IgE production represent the sensitization phase of allergic reaction
- IL-4 and IL-13 are essential to induce class switching to IgE in B cells and for the production of allergen-specific IgE antibodies
- Cross-linking of the IgE-FcεRI complexes on basophils and mast cells and subsequent release of anaphylactogenic mediators is responsible for the immediate hypersensitivity reaction
- Effector T and B cell and eosinophil infiltration of the affected tissues is controlled by a chemokine network
- Type 2 innate lymphoid cells play a role in eosinophilic inflammation in mouse models and are observed in nasal polyp tissue in humans
- There is strong evidence on the defective allergen tolerance mechanisms by T and B regulatory cells
- Epithelial barrier is leaky in asthma, chronic rhinosinusitis and atopic dermatitis
- Different disease endotypes show different dominant molecular mechanisms, biomarkers and therapy response to biologicals

The immune system forms an interactive network with tissues and makes its decisions on the basis of signals coming from resident tissue cells, infectious agents, commensal bacteria and almost any environmental agents. The immunologic basis of allergic diseases (Table 1) is observed in two phases: sensitization and development of memory T and B cell responses and IgE production and effector functions related to tissue inflammation, tissue injury, tissue remodeling and chronicity in asthma, atopic dermatitis (AD) and allergic rhinitis (AR). Different disease endotypes may become apparent with different dominant molecular mechanisms, related biomarkers and response to biological therapy.

In the sensitization phase, during the development of allergic diseases, effector Th2 cells produce IL-4, IL-5, and IL-13. IL-4 and IL-13 induce class switching to the ε immunoglobulin heavy chain in B cells and the production of allergen-specific IgE antibodies (Figure 1). Innate lymphoid cells (ILC2) also provide Th2 cytokines. Allergen-specific IgE binds to the high-affinity FcεRI on the surface of mast cells and basophils, thus leading to the patient's sensitization. **In the effector phase**, when a new encounter with the allergen causes cross-linking of the IgE-FcεRI complexes on sensitized basophils and mast cells, they are activated and subsequently release anaphylactogenic mediators that are responsible for the immediate hypersensitivity reaction.

Defective epithelial barrier function has been demonstrated for bronchial epithelial cells in the asthmatic lung, epithelial cells in the sinus tissue of chronic rhinosinusitis (CRS) patients as well as keratinocytes in the skin of AD patients. Recent studies suggest that tissue integrity is disturbed and allows penetration of allergens, bacterial toxins and other particles through the epidermis, the lung and sinus epithelium, where they may activate the immune system leading to severe chronic inflammation in these diseases. Activation of the epithelial cells and release of IL-25, IL-31, IL-33 and TSLP contribute to type

TABLE 1

Cellular and molecular events in allergic inflammation
• Epithelial barrier defect in the skin and affected mucosas
• Epithelial cell activation and their proinflammatory cytokines and chemokine production that induces inflammation and contributes to Th2 response: TNF-α, IL-13, IL-25, IL-31, IL-33, TSLP
• Chemokine release attracting Th2 cells and eosinophils
• Epithelial apoptosis and shedding in AD and asthma: IFN-γ, TNF-α, IL-32
• Innate lymphoid cell type 2 response: IL5, IL13
• Th2 response: IL-4, IL-5, IL-13,
• Eosinophilia: IL-5, IL-25, IL-33
• Local and systemic IgE production: IL-4, IL-13
• Cross-linking of IgE receptor FcεRI on the surface of mast cells and basophils and their degranulation
• Smooth muscle, myofibroblasts activation, bronchial hyperreactivity in asthma: IL-4, IL-9, IL-13, IL-25, IL-33
• Angiogenesis in chronic inflammation: VEGF, IL-32
• Survival and reactivation of migrating inflammatory cells and their interaction with resident tissue cells and other inflammatory cells: IL-2, IL-4
• Activation of other effector T cell subsets, such as Th9, Th17 and Th22 cells and their contribution to mucus production, tissue inflammation and regeneration.

2 responses of T cells and innate lymphoid cells (Figure 2). These cytokines play a role in the production of allergen-specific IgE, eosinophilia, permissiveness of endothelium for the recruitment of inflammatory cells to inflamed tissues, production of mucus and decreased threshold of contraction of smooth muscle cells.

The discovery of ILCs has changed our perception of T cells as the major cytokine-secreting effectors of immunity and made us aware of completely unappreciated innate immune cell sources of effector cytokines. Particularly type 2 ILCs can contribute to Th2 type inflammation similar to Th2 cells in mouse models. Th1 cells also efficiently contribute to the effector phase in allergic diseases with their role in apoptosis of the epithelium in asthma and AD.

In recent years, induction of **immune tolerance** has become a

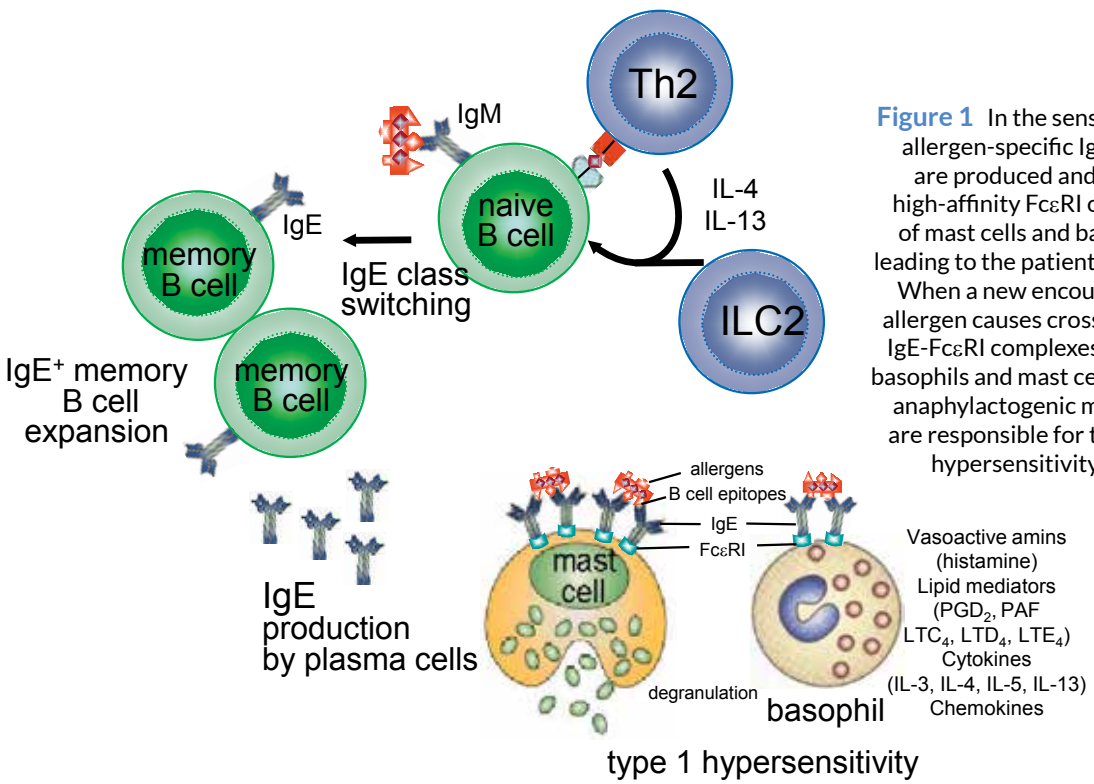


Figure 1 In the sensitization phase allergen-specific IgE antibodies are produced and bind to the high-affinity FcεRI on the surface of mast cells and basophils, thus leading to the patient's sensitization. When a new encounter with the allergen causes cross-linking of the IgE-FcεRI complexes on sensitized basophils and mast cells, they release anaphylactogenic mediators that are responsible for the immediate hypersensitivity reaction.

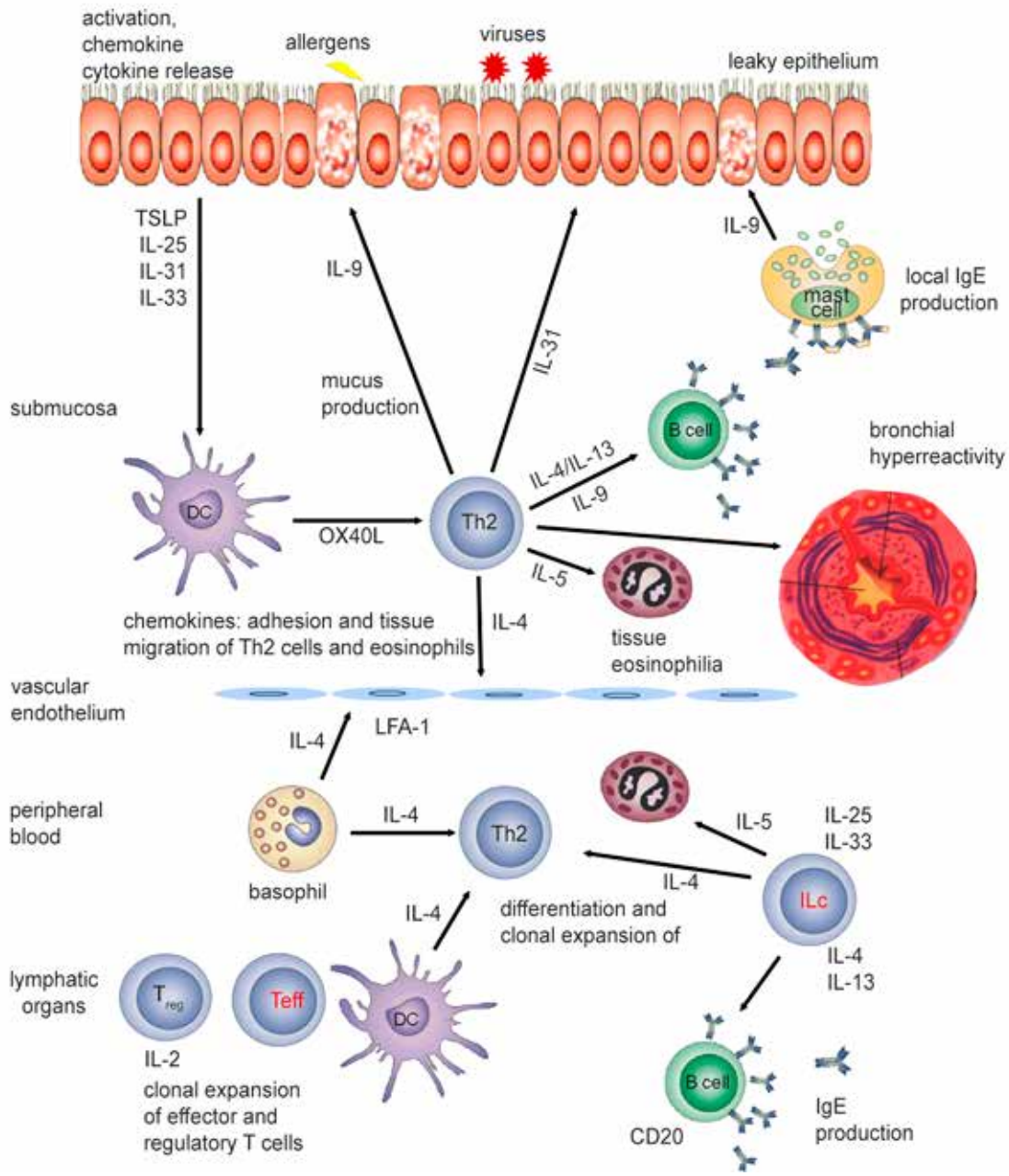
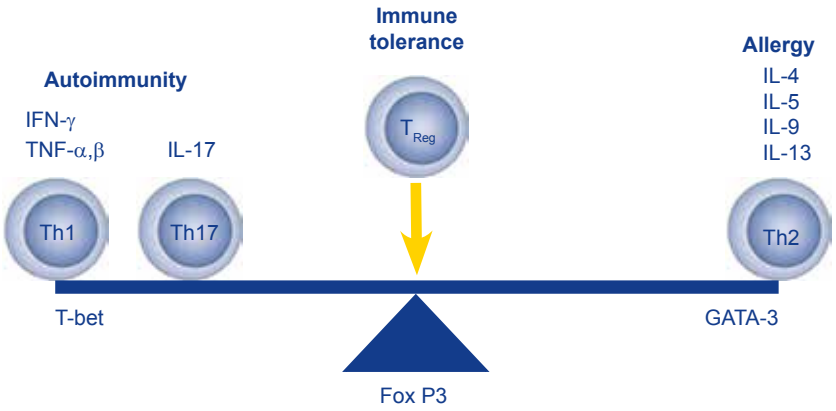


Figure 2 Pathogenic mechanisms in allergic inflammation. Epithelial leakiness and activation and their proinflammatory cytokines and chemokines (TNF-α, IL-13, TSLP, IL-31, IL-33) production induces inflammation and contributes to Th2 response. Highly activated epithelial cells undergo apoptosis and shedding takes place. Chemokines are essential players for the recruitment of inflammatory cells, which is followed by survival and reactivation of migrating inflammatory cells and their interaction with resident tissue cells and other inflammatory cells. Innate lymphoid cells (ILC2) play a role in T and B cell activation and recruitment and are early providers of Th2 and T cell recruitment cytokines. Th2 type of an immune environment is characterized by IL-4, IL-5, IL-9, IL-13, IL-25, IL-33 production coming from Th2 cells and tissue cells. Eosinophilia is induced by IL-5, IL-25, IL-33. Local and systemic IgE production takes place in allergic patients with the involvement of IL-4, IL-13. Other effector T cell subsets, such as Th9, Th17 and Th22 cells also play partial roles in inflammation, mucus production and tissue healing. Smooth muscle, myofibroblasts activation and bronchial hyperreactivity is related to IL-4, IL-9, IL-13, IL-25, IL-33. Several chemokines, and arachidonic acid pathway molecules and other small molecules play roles in the inflammatory cell recruitment and further augmentation of the inflammatory cascades.



	Th1	Treg	Th2
Transcription factors	T-bet	FoxP3	GATA-3
Major functions	Delayed type of hypersensitivity, macrophage activation limited B cell help/ inhibition	inhibition of Th1 and Th2 cells inhibition of mo/mac inhibition of DC maturation peripheral tolerance	chronic eosinophilic inflammation with high IgE
Beneficial role	Chronic intracellular infections: leishmaniasis, leprosy, virus infections	immunotherapy transplantation autoimmunity allergy/asthma pregnancy	arthritis autoimmunity helminth inf. pregnancy

Figure 3 Concept development in T cell tolerance in allergy and autoimmunity. After the discovery of Th1 and Th2 cell subsets in 1986, it was thought that Th1 cells play a role in infections and autoimmunity and Th2 cells in allergic disease. Both subsets were considered to have reciprocal roles in counter regulating each other. After the introduction of Treg cells, it was demonstrated that although there is reciprocal regulation between individual Th cell subsets, Treg cells play a major role in the induction of immune tolerance in allergy, autoimmunity, organ transplantation, cancer, pregnancy, chronic infections.

prime target for prevention and treatment strategies for allergic diseases. Immune tolerance to allergens can be defined as establishment of a long-term clinical tolerance against allergens, which immunologically implies changes in memory type allergen-specific T and B cell responses as well as mast cell and basophil activation thresholds that do not cause allergic symptoms anymore (Figure 3). T and B regulatory cells and production of allergen-specific IgE-blocking IgG4 isotype antibodies play an essential role in allergen tolerance. Similar mechanisms of immune tolerance take place in high dose allergen exposed bee-keepers and cat owners (who do not develop allergy), after allergen-specific immunotherapy, and in individuals who naturally outgrow allergic diseases.

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5 INNATE IMMUNE RESPONSE IN ALLERGY

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KEY MESSAGES

- Bronchial epithelial cells and skin keratinocytes play an important role in asthma and atopic dermatitis
- Type 2 innate lymphoid cells are essential for asthma progression
- Dendritic cell subsets may play both pro and anti-inflammatory roles
- Epithelial cells, dendritic cells and innate lymphoid cells play a crucial role during the chronic phase of the allergic inflammation by producing pro-inflammatory cytokines and chemokines that attract other inflammatory cells to affected tissues
- Non-antigen specific innate immunity serves as the bridge to adaptive immune responses

While the underlying inflammation in allergic asthma, allergic rhinitis and atopic dermatitis is thought to result from the activity of Th2 cells, the innate (non-antigen specific) response to these insults provides key triggers for the initiation of the chronic inflammation.

Innate immune responses begin with sensing of insults by airway and skin epithelial cells. Non-specific antigen recognition by epithelial cells occurs via pattern recognition receptors (PRR), which include both soluble (collectins) and cellular [Toll-like receptors (TLR)] PRRs. Soluble PRRs recognize the carbohydrate moieties of microbes and can activate the complement cascade, initiating inflammatory responses. Cellular PRRs are better known for their interaction with pathogen-associated molecular patterns (PAMPs). Although TLRs are best known for binding to products of microbes and viruses, allergens also interact with TLRs (e.g., house dust mite protein, Der p2 with TLR4). Binding of TLRs and other cellular PRRs triggers the production of interferon (IFN) and pro-inflammatory cytokines and chemokines. Both type I and type III IFN production are important for antiviral defense. Airway epithelial cells from subjects with asthma have decreased levels of IFN production after viral infection, suggesting that IFN may play a protective role in preventing viral asthma exacerbations. Production of pro-inflammatory cytokines / chemokines (e.g., TNFα, IL-1, IL-6, IL-25, IL-33, TSLP) from epithelial cells is the result of PRR activation of NFκB.

Epithelial cells responding to allergen insult also produce IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) (Figure 1). These cytokines have downstream effects on innate and adaptive immune cells. In particular, type 2 innate lymphoid cells (ILC2, Neucytes) are important for asthma pathogenesis. ILC2 are derived from a common lymphoid progenitor and related to NK and RORγt innate lymphoid cells (Figure 2). ILC2 respond to IL-25, IL-33, and TSLP stimulation by producing high levels of "Th2-type" cytokines (i.e., IL-5, -9, and -13) upon stimulation. These cytokines can then activate eosinophils (via IL-5, -13) and mast cells (via IL-9) as well as B and T lymphocytes (Figure 1). In addition, secretion of IL-13 induces mucus production, smooth muscle contractility, and alternative activation of alveolar macrophages, which leads to amplification of IL-33 production. ILC2 also secrete amphiregulin,

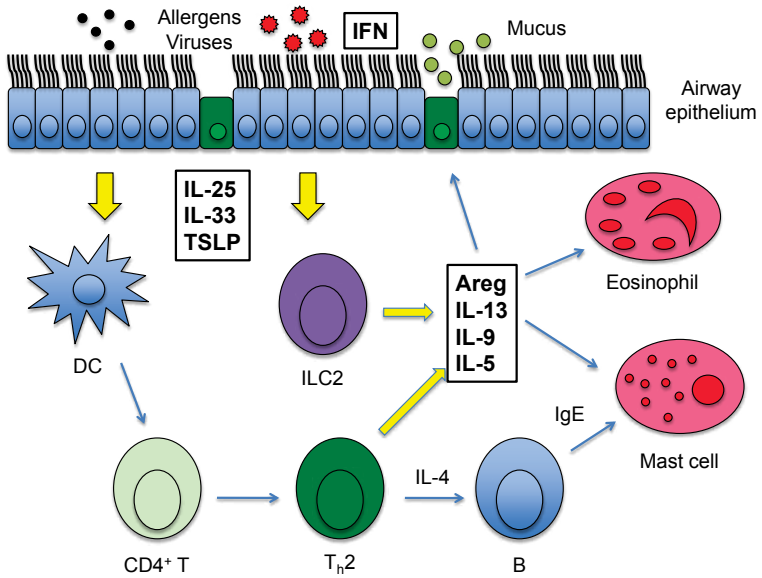

Figure 1 Innate immune response in asthma. Exposure to allergens or viruses induces innate immune responses in airway epithelial cells. Viral infection induces type I and type III interferon (IFN) responses. Epithelial cells also secrete IL-25, IL-33, and TSLP, which activate type 2 innate lymphoid cells (ILC2) and dendritic cells (DC). ILC2 cells produce "Th2-like" cytokines (e.g., IL-5, IL-9, and IL-13). These cytokines then active eosinophils, mast cells, and goblet cells to cause disease. ILC2 also produce amphiregulin (Areg) to induce airway remodeling. Activated DC traffic to lymphoid organs to initiate T cell responses to the allergens/viruses to further disease pathogenesis. Adapted from ref. 3.

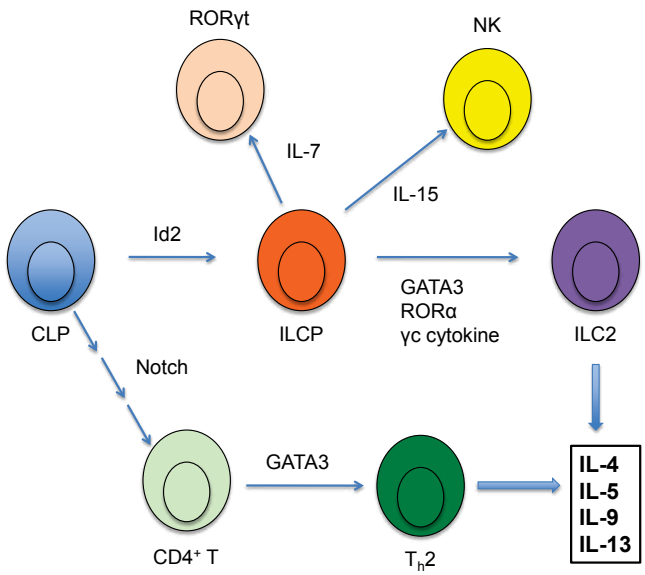

Figure 2 Differentiation of ILC2 cells. ILC precursors (ILCP) are derived from the common lymphoid progenitor (CLP) cells in an Id2-dependent process. ILCP are further differentiated into RORγt, NK, and ILC2 cells through the activities of transcription factors (GATA3, RORα) and cytokines (IL-7, IL-15). CLP cells also differentiate into Th2 cells through thymic maturation. ILC2 and Th2 cells secrete an overlapping set of cytokines. Adapted from ref. 3.

which may be involved in airway remodeling. TSLP also drives the maturation of immature lung dendritic cells (DC) to conventional DC capable of presenting antigen to T cells. These allergen-activated DC then initiate the adaptive immune responses characteristic of atopic airway disease.

In summary, innate immunity plays a key role in initiating asthma. Recognition of insults by AEC leads to activation of ILC2, which produce Th2-type cytokines, and DC, which stimulate allergen-specific CD4⁺ T cell responses is necessary for asthma progression.

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6 DENDRITIC CELLS

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KEY MESSAGES

- Dendritic cells are one of the first immune cells that come into contact with allergens at mucosal surfaces and can sample luminal antigens directly by extending dendrites across the epithelial barrier
- In the lymph node they report on the type of antigen encountered and subsequently induce CD4 T helper cell differentiation and CD8 T cell activation and transfer some of their encountered antigens to B cells
- Lung and skin DCs also play a crucial role during the chronic phase of the allergic inflammation, by producing chemokines that attract other inflammatory cells to inflamed tissues
- Unraveling how DCs induce and maintain Th2 immunity will provide new selective therapeutics targets for allergic diseases

The adaptive immune response to allergens is characterized by a humoral arm (production of IgE by B lymphocytes), and a cellular arm (CD8 and CD4 T lymphocytes that respond to the allergen in the context of MHCI and MHCII molecules). Before adaptive immunity is induced to environmental or food allergens, the allergen must get through the natural barriers of the body (skin, mucus membranes) and reach the cells of the immune system that are recirculating in the lymph nodes (LN). Dendritic cells (DCs) are one of the first immune cells that come into contact with allergens at mucosal surfaces. In the lungs, intestine and skin, DCs sit at the basolateral side of epithelial cells and can sample luminal antigens directly by extending dendrites across the epithelial barrier (Figure 1).

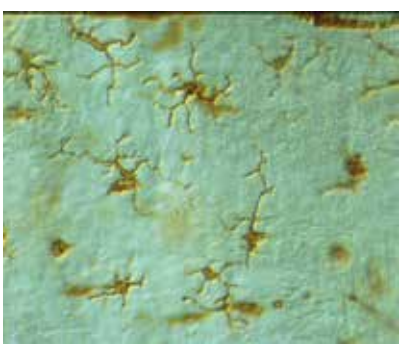

Figure 1 Dendritic cells across the epithelial barrier.

After antigen uptake, DCs migrate to the draining LN and present the processed antigen to naïve T cells, leading to clonal expansion and differentiation of antigen-specific T cells (Figure 2). Dendritic cells arriving in the LN report on the type of pathogen or allergen that has been encountered in the periphery, and they subsequently induce CD4 T helper cell differentiation (Figure 3), CD8 T cell activation and transfer some of their encountered antigens to B cells.

DCs originating from the lungs of house dust mite (HDM) allergen-exposed mice are necessary and sufficient to induce Th2 sensitization to HDM. Lung and skin DCs also play a crucial role during the chronic phase of the allergic response, by producing chemokines that attract other inflammatory cells back to peripheral tissues (Figure 2). In addition, allergen-specific IgE and IgG1, through stimulation of FcεRI and FcγRIII respectively, target allergens to DCs thus boosting Th2 immunity further. During both sensitization and challenge, DCs closely communicate with neigh-

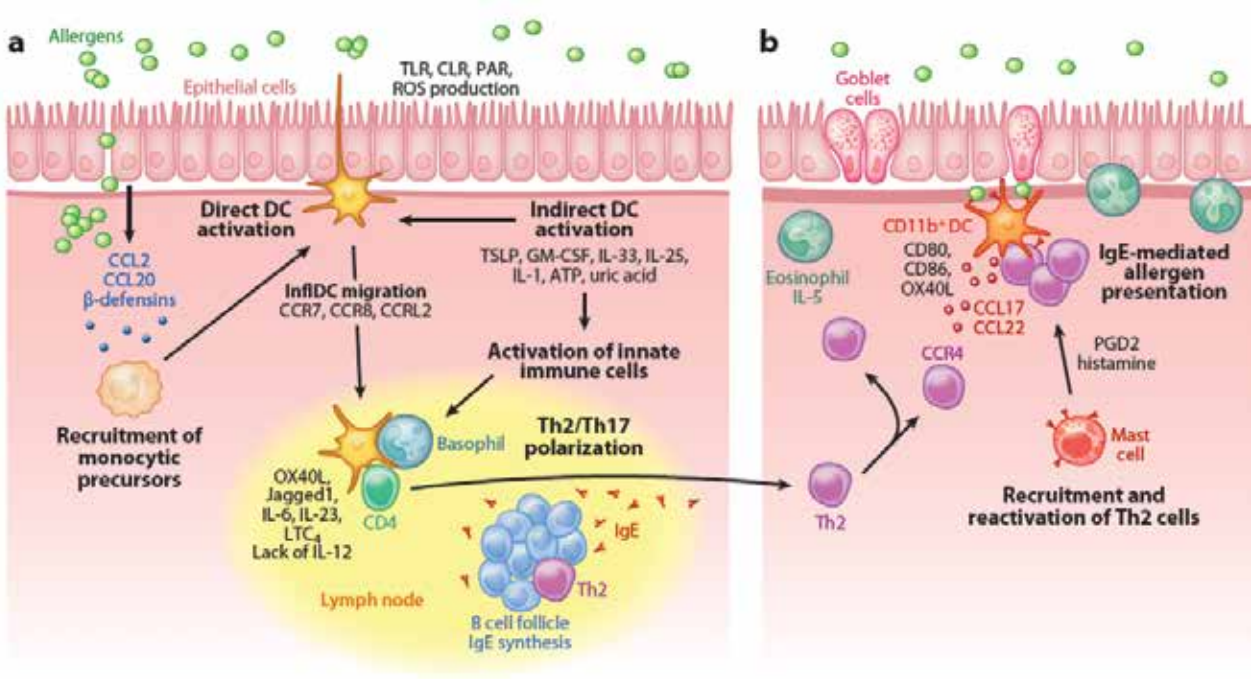

Figure 2 Role of dendritic cells in inflammation and T-cell polarisation.

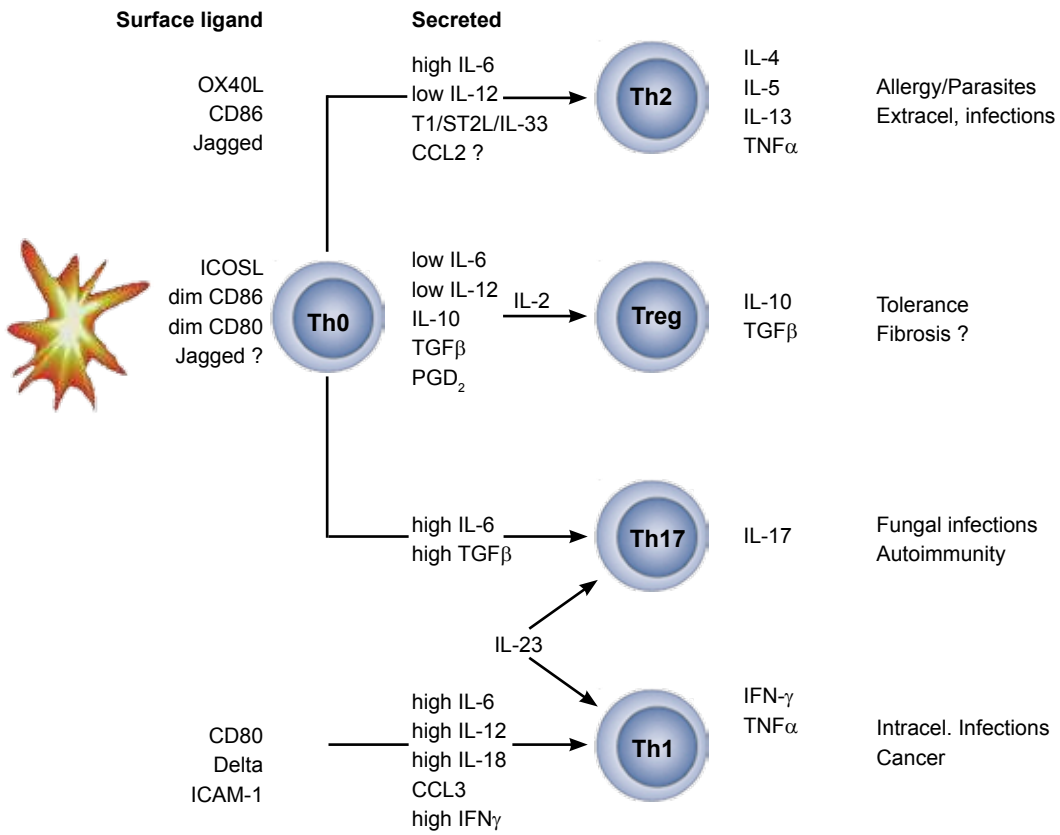

Figure 3 Factors that affect T-cell differentiation.

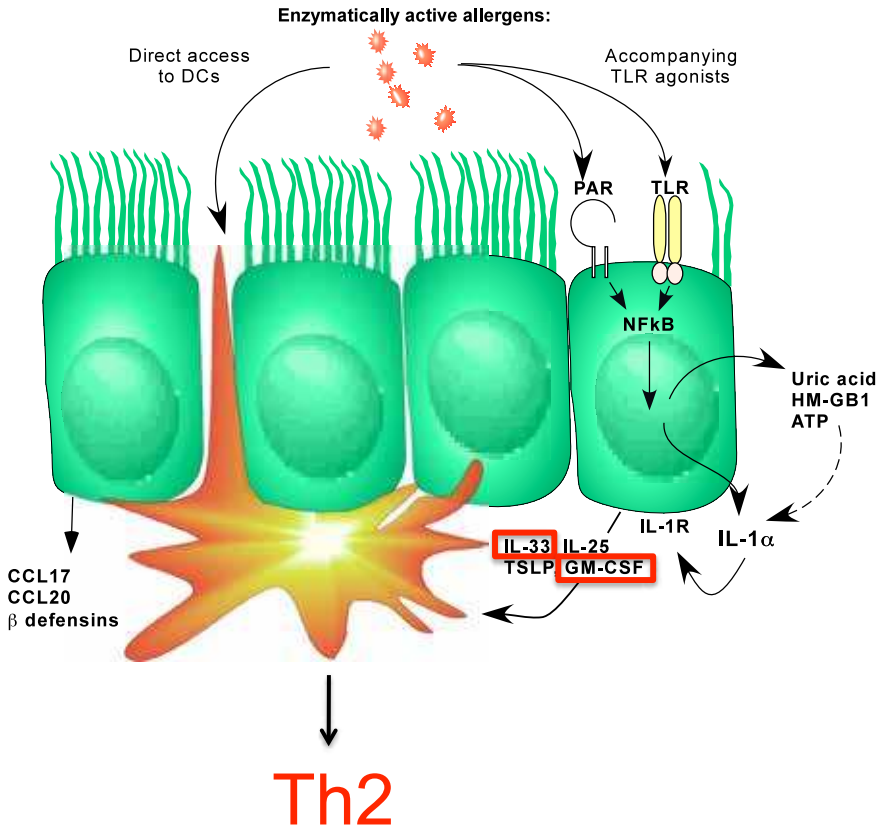

Figure 4 The interaction of dendritic cells and epitelial cells drives the inflammatory process.

boring epithelial cells. Triggering of pattern recognition receptors on epithelial cells like the Toll-like receptor 4 or protease activated receptors by allergens leads to the production of epithelial-derived chemokines and cytokines (Figure 4) that recruit DCs and that program the DCs to induce Th2 immune responses. Epithelial cells and other innate immune cells also make endogenous danger signals like uric acid, ATP and High Mobility Group Box 1 (HM-GB1) that can have the same effect on DCs.

Patients with atopic dermatitis, allergic rhinitis and asthma have increased numbers of activated DCs armed with IgE in the inflamed tissues. Not surprisingly, targeting the function of DCs in allergy constitutes a therapeutic avenue. However, eliminating the function of DCs completely would also induce immunodeficiency, and it is much more important to unravel how DCs induce and maintain Th2 immunity selectively, to find new therapeutics for allergy.

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7 NATURAL KILLER CELLS AND NATURAL KILLER-T CELLS

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KEY MESSAGES

- Natural Killer (NK) cells display a potent regulatory function by secreting various cytokines or cell-to-cell contact and thus, regulate innate and adaptive immune responses and maintain immune homeostasis
- NK cells express subsets similar to T helper cells, such as NK1, NK2 and NK regulatory cells
- Understanding the mechanisms enrolled in the development of allergic diseases are essential to develop strategies for treatment and prevention
- Recent developments in NK cell subsets support their role in allergic diseases

Besides the heterogeneity of asthma pathogenesis, current knowledge underlines the dominance of a subgroup with Th2-like immune response and eosinophilia. However allergic asthma may additionally involve innate, T cell independent immune responses. Several different populations of innate lymphoid cells (ILC), including natural killer (NK) cells, γδ T cells, and CD1-restricted NK1 cells have been previously implicated in the regulation of immune responses in the respiratory tract.

NK cells are innate lymphocytes, which are a first line of defense against infection and cancer. The airways are a major route of entry of many important pathogens into the body and the ability of NK cells to respond rapidly to infection suggests an important role for these cells in acute pulmonary infection. Recent developments in our understanding of NK cell subsets support their role in allergic diseases that may contribute to allergen-specific Th1 or Th2 cell generation as well induction or suppression of IgE. The *in vivo* and *in vitro* existence of human NK cell subsets, similar to Th1 and Th2 cells, with distinct cytokine patterns as IFN-γ secreting and IFN-non-secreting NK cells strongly support this concept (Figure 1). The IFN-γ secreting NK subset showed a typical Th1-like cytokine pattern. In contrast, the IFN-γ-non-secreting NK subset was composed of IL-4, IL-5 and IL-13-producing NK cells. These results demonstrate that circulating NK cells retain effector subsets in humans with distinct cytokine profiles and may display different inflammatory properties. In addition, it has been reported that patients with allergic rhinitis had a higher percentage and cytotoxicity of NK cells compared to nonatopic patients. The mean percentage of IL-4- and IL-13-secreting NK cells were significantly higher, while IFN-γ^+ NK cells were not significantly lower in allergic rhinitis patients compared to nonatopic controls. Since NK cells are important cells in innate immunity and the initiation of immune responses, their different cytokine patterns may be important in changing the cytokine milieu and the induction of T cell deviation.

Natural killer-T (NK-T) cells are unique CD1d-restricted T cells with NK cell surface markers. These cells may play an important role in the pathogenesis of asthma. Invariant NK-T cells and not conventional MHC class II-restricted $CD4^+$ T cells were found predominant in the lungs and bronchoalve-

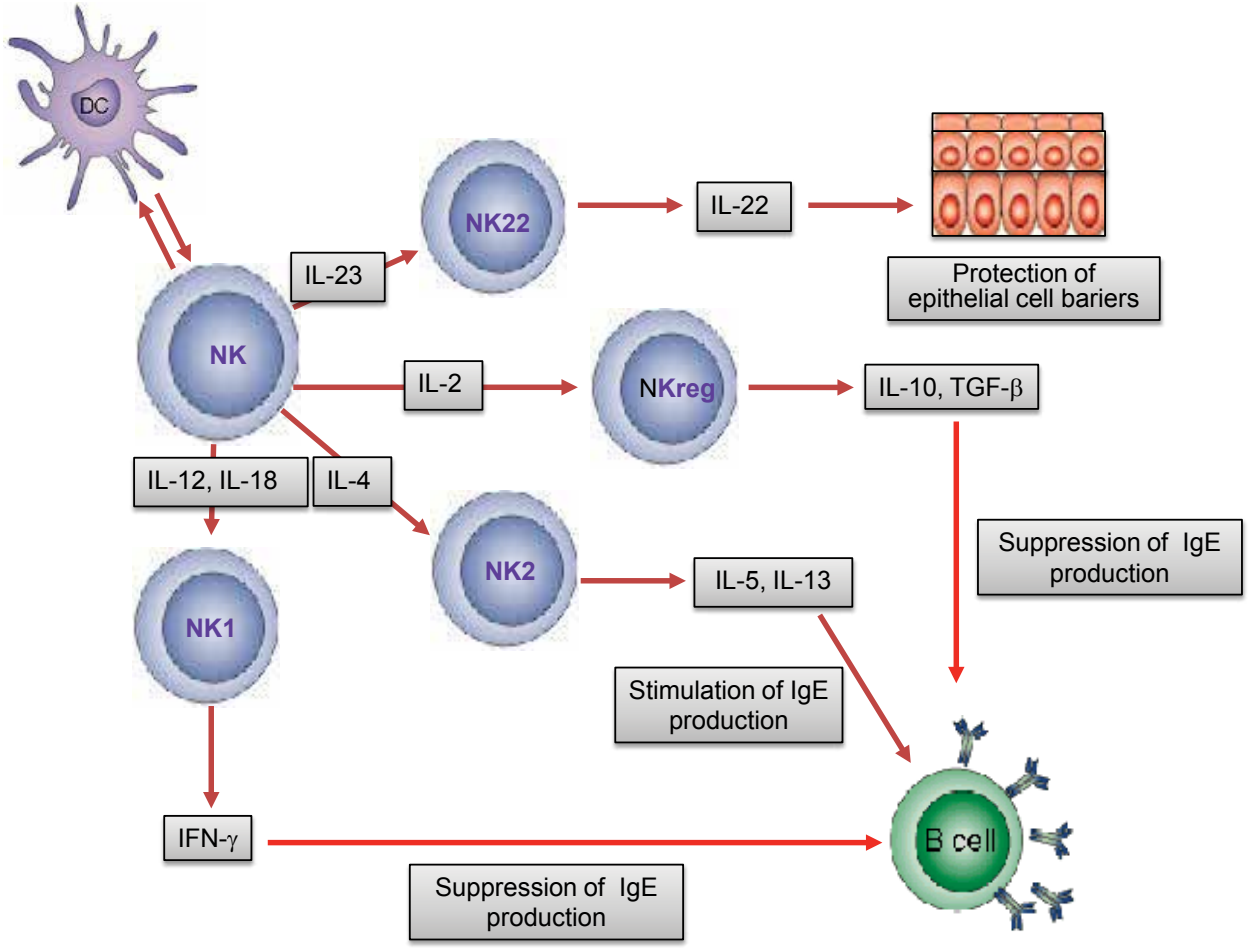

Figure 1 NK cells are divided into four different subsets according to their cytokine secretion. NK cells have been detected in close contact to dendritic cells. NK cells grown in IL-12 and IL-18 (NK1) produce IFN-γ and inhibit IgE production, whereas NK cells grown in IL-4 (NK2) produce IL-5 and IL-13 and stimulate IgE production. NK reg cells produce IL-10 and TGF-β and suppress IgE production. IL-22 secreting NK22 subset might have a role in the protection of epithelial cell barriers. (*Reprinted from J Allergy Clin Immunol, 132/3, Deniz G,van de Veen W, Akdis M. Natural killer cells in patients with allergic diseases, 527-35, Copyright 2013, with permission from Elsevier.*)

olar lavage fluid of allergic asthma. Although CD1d-restricted NK-T cells might play a role in modulating the asthmatic phenotype, they are not the critical drivers of the asthmatic response and at most play a modulatory role.

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8 INNATE LYMPHOID CELLS

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KEY MESSAGES

- Innate lymphoid cells (ILCs) have lymphoid morphology, but lack rearranged antigen receptors and myeloid and dendritic cell markers
- ILCs are derived from a committed ILC precursor
- Group 1 ILCs (ILC1s) release INF-γ, but not Th2 and Th17 cytokines under the influence of IL-12 and IL-18
- Group 2 ILCs (ILC2s) may play a role in allergic diseases and eosinophilic inflammation by releasing the Th2 cytokines IL-5, IL-9 and IL-13, when stimulated with IL-25, IL-33 and thymic stromal lymphopoietin
- Group 3 ILCs (ILC3s) may play a role in some chronic allergic diseases by releasing the Th17 cytokines IL-17 and IL-22

DEFINITION AND ONTOGENY

Innate lymphoid cells (ILCs) are the cells having lymphoid morphology, but lacking recombination activating gene (RAG)-dependent rearranged antigen receptors. They also lack myeloid and dendritic cell markers (Lineage – (Lin-)). According to these definition, natural killer (NK) cells and lymphoid tissue-inducer (LTi) cells are included into the ILC population. NK cells mediate initial immune responses against viruses and cancer cells. LTi cells are essential for the formation of lymph nodes.

ILCs can be divided into three groups. Group 1 ILCs (ILC1s) are defined by their capacity to produce Th1 cytokine IFNγ and the inability to produce Th2 cell- and TH17 cell-associated cytokines. They develop under the influence of IL-12 and IL-18. Group 2 ILCs (ILC2s) are capable of producing Th2 cytokines (IL-5, IL-9 and IL-13) in response to epithelium-derived cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). Group 3 ILCs (ILC3s) can produce Th17 cytokines IL-17 and/or IL-22 in the presence of IL-1β and IL-23. Some ILC3s express the natural cytotoxicity triggering receptor (NCR) NKp46 (NCR+ ILC3s). The NCR+ ILC3s can produce IL-22, but not IL-17, while NCR-- ILC3s are capable of producing IL-17, but not IL-22. However, it should be noted that some NCR--ILC3s can also produce IL-22. Recently, it was suggested that ILCs are derived from a committed ILC precursor, which is developmentally unrelated to NK and LTi cells.

ROLE OF ILCS IN ALLERGY

ILC2s include Lin- SCA1+ natural helper cells found in fat-associated lymphoid clusters, Lin-SCA1+ nuocytes and Lin-SCA1- innate helper 2 cells derived from lymph nodes of IL-25 and/or IL-33-injected or N. brasiliensis-infected mice. ILC2s are important in host resistance against nematodes. Although Th2 cells are a major source of type 2 cytokines during asthmatic and allergic reactions, ILC2s also contribute to disease pathology, especially where IL-25, IL-33 and TSLP are released by inflamed and damaged epithelia. Human ILC2s have similar properties with their murine counterparts. In addition, human ILC2s express CRTh2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) on their surface.

IL-17-producing ILC3s play a role in neutrophilic inflammation in a particular endotype of asthma via production of IL-1β by macrophages stimulated with damage-associ-

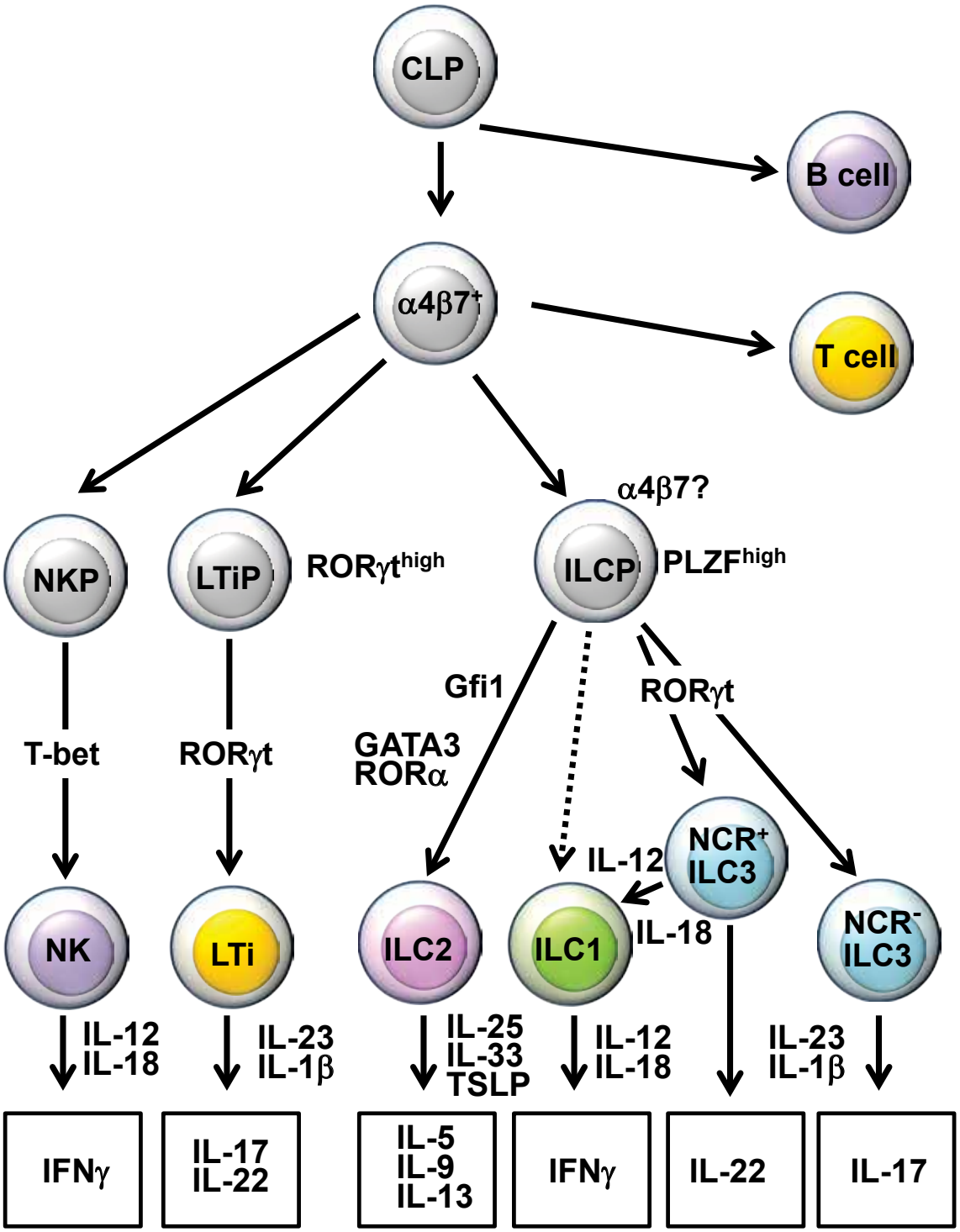

Figure 1 Ontogeny of innate lymphoid cells (ILCs). A committed ILC precursor (ILCP) having a high level of transcriptional factor PLZF (2) can give rise to ILC1s, ILC2s and ILC3s, but not to LTi cells and NK cells, which originate from a α4β7+ common progenitor shared with the three ILC lineages. Development of ILC2s depends on the transcription factors Gfi1, GATA3 and RORα. ILC3s require the transcription factor RORγt for their development and function. Although NCR+ ILC3s can give rise to ILC1s if stimulated with IL-12 and IL-18, the differentiation pathway of ILC1s is not fully understood yet.

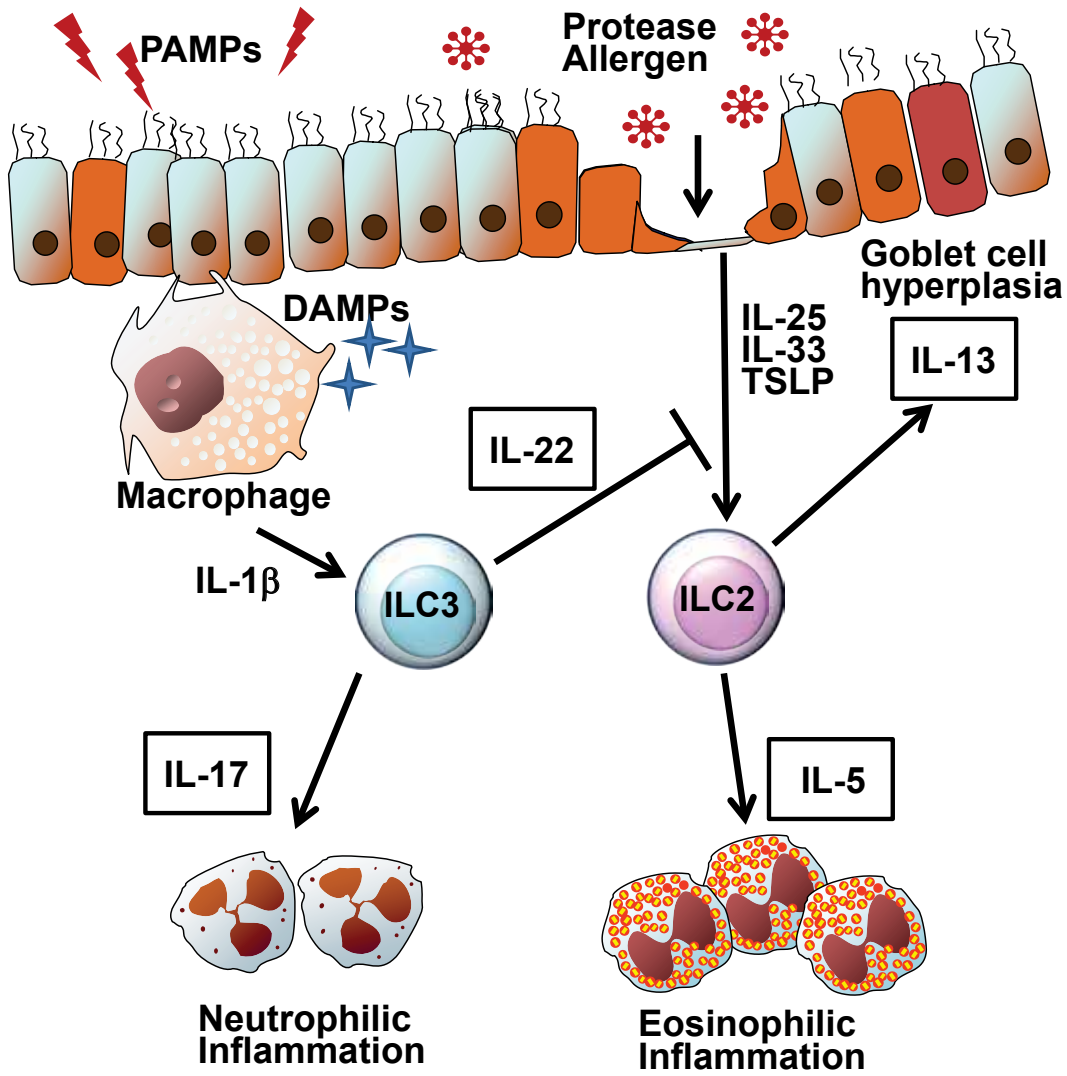

Figure 2 The role of ILCs in allergy. Epithelial tissues can release IL-25, IL-33 and TSLP in response to protease allergens such as house dust mites or papain, DAMPs, PAMPs and TH2 cytokines. In response to the epithelium-derived cytokines ILC2s can release IL-13, which induces inflammation and remodeling (such as goblet cell hyperplasia) in the tissue, and IL-5, which can induce eosinophilic inflammation. ILC3s release IL-17, which can induce neutrophilic inflammation, and IL-22, which inhibits the release of ILC2-activating cytokines.

ated molecular patterns (DAMPs) and/or pathogen-associated molecular patterns (PAMPs). The expression of the IL-10 family cytokine IL-22, which is capable of being released from ILC3s, LTi cells or Th17 cells, is increased in chronic allergic inflammation in the lung and skin. IL-22 inhibits the production of ILC2-activating cytokines, IL-25 and IL-33.

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9 MAST CELLS

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KEY MESSAGES

- Mast cells develop in essentially all tissues from precursors that circulate in the blood
- Mast cells are major sources of histamine and other products (mediators) that contribute to anaphylaxis and other allergic disorders
- Mast cells can be rapidly activated (within minutes) to release mediators when allergens are recognized by IgE antibodies bound to IgE receptors (FcεRI) on the cells' surface
- Mast cells also can be activated to release mediators by many agents that act independently of IgE
- Mast cells can have beneficial roles in enhancing resistance to animal venoms and in host defense against certain parasites

WHAT ARE MAST CELLS?

In humans and other vertebrates, mast cells reside in virtually all tissues, often close to epithelial surfaces (e.g., the skin, respiratory system, and gastrointestinal tract) and near blood vessels, nerves, smooth muscle cells and fibroblasts. Mast cell precursors are generated in the bone marrow, circulate in the blood, and then enter the tissues where they complete their maturation, becoming cells with many prominent cytoplasmic granules (Figure 1A & C). These granules are storage sites for mast cell products (often called "mediators") that, when released by the cell, have powerful effects on other cell types. Mast cell granules contain most of the body's histamine and virtually all of its heparin, as well as a variety of proteases (Table 1). When mast cells are "activated" (i.e., stimulated to release their products), they release histamine, heparin and proteases by "degranulation" (Figure 1B & D), and they also secrete many other mediators that are not stored, but are synthesized by the activated cells, including leukotrienes, prostaglandins, cytokines, chemokines and peptide growth factors (Table 1). Mast cell numbers can increase in tissues at sites of allergic diseases or parasite infections, and in other settings.

HOW CAN MAST CELLS BE ACTIVATED TO RELEASE THEIR PRODUCTS?

Mast cells express on their surface hundreds of thousands of high affinity receptors (FcεRI) that strongly bind the Fc portion of IgE antibodies. Individual mast cells can bind IgEs which recognize any of a variety of different allergens derived from pollens, foods, dust mites, medicines, etc. Such mast cells can be activated when they encounter any antigens that cross-link two adjacent IgE molecules, which results in aggregation of the IgE-bound FcεRIs, signaling the cells to release their products (Figure 1B & D). Mast cells also can be activated independently of IgE, e.g., by products of microorganisms, certain neuropeptides, and compounds present in animal venoms (Table 2).

When large numbers of mast cells are rapidly activated by the systemic distribution of an allergen in subjects who have IgE recognizing that allergen, anaphylaxis can occur within minutes. Such IgE-dependent anaphylaxis is absent or markedly diminished in mice genetically lacking mast cells (even though they have basophils, another bone marrow-derived cell

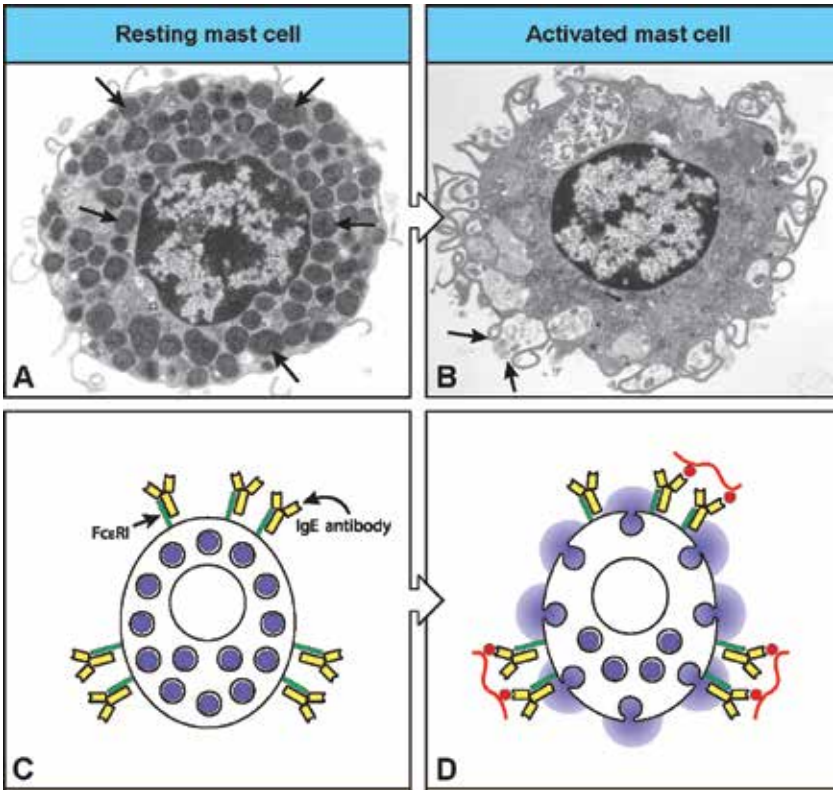

Figure 1 (A, C) A resting mast cell (shown in a transmission electron micrograph in A and as a cartoon in C) contains many cytoplasmic granules (indicated by arrows in A) and has allergen-specific IgE (yellow symbols in C) bound to FcεRI receptors (green symbols in C) on its surface (B, D). When allergen (red symbols in D) is recognized by adjacent IgE antibodies bound to the mast cell's FcεRI receptors, this aggregates the FcεRIs on the cell's surface, activating the mast cell to release its granule contents at points where the granules fuse with the plasma membrane (indicated by arrows in a transmission electron micrograph in B and as a cartoon in D). Such activated mast cells also secrete newly synthesized products that are not stored in the granules. (Modified from Fig. 9.44 in Parham P. The Immune System. 3rd edition, Copyright 2009 from The Immune System by Parham. Reproduced by permission of Garland Science/Taylor & Francis LLC. The electron micrographs in A & B are courtesy of Ann M. Dvorak.)

TABLE 1

Mast Cell Products

	Products	Biological effects*
Stored preformed in granules and secreted upon activation (in minutes)	Histamine	• Increases vascular permeability and blood vessel dilatation • Contracts airway smooth muscle • Causes itching and pain • Influences immune responses and the function of some nerves
	Heparin	• Anticoagulant • Required for storage of other products in granules
	Proteases (e.g., tryptase, chymase, carboxypeptidase A3)	• Degrade certain proteins and peptides, including components of animal venoms • Regulate tissue remodeling • Converts angiotensin I to angiotensin II (chymase)
Synthesized and secreted upon activation (beginning in minutes for lipid mediators, extending over hours for peptide products†)	Lipid mediators (e.g., leukotrienes, prostaglandins)	• Regulate migration and function of leukocytes • Increase vascular permeability • Induce constriction or dilatation of blood vessels (depending on the type of mediator) • Contract or relax smooth muscle (airways, gastrointestinal tract) • Enhance mucus secretion
	Cytokines, chemokines, peptide growth factors	• Many effects on other cells (both leukocytes and tissue structural cells) that can promote or suppress inflammation and/or tissue remodeling

* *Only some of the many biological effects of these products are listed.*

† *Some of these can be present in granules and therefore also can be released rapidly upon mast cell activation.*

TABLE 2

Mechanisms of mast cell activation*

Activation mechanisms†	Settings in which this occurs	Comments
Cross-linking of IgE bound to mast cell surface FcεRI by multivalent antigen recognized by the IgE	Anaphylaxis, allergic rhinitis, atopic dermatitis, allergic asthma, some types of urticaria	The site of mast cell activation depends on the site of exposure to the antigen; in anaphylaxis, there is systemic distribution of the offending antigen throughout the body.
Reaction of microbial products or products of damaged or dead cells with receptors (Toll-like receptors or other pattern recognition receptors) on the mast cell surface or inside the mast cell	Various types of viral or bacterial infections; diverse settings in which cell damage or cell death occurs	Exposure of mast cells to some of these products cells can influence how the mast cells respond to other activation signals, such as IgE and antigen.
Reaction of endogenous peptides with receptors for those peptides on the mast cell surface	Various disease processes or mechanisms of host defense that maintain health	Endogenous peptides that can activate some types of mast cells include certain neuropeptides, endothelin-1, and products of complement activation (C3a, C5a).
Reaction of exogenous peptides with receptors on the mast cell surface that recognize such peptides	Envenomation by venomous reptiles	Some of these venom peptides are structurally similar to endogenous peptides that can also activate mast cells; mast cell proteases released when the activated mast cells degranulate can degrade and thereby reduce the toxicity of some components of the venoms.

** In addition to mechanisms that activate mast cells, certain stimuli can diminish the extent of mast cell activation.*

† Mast cells activated by IgE and specific antigen can release many or all of the products listed in Table 1. By contrast, other activation mechanisms can result in the relatively selective release of granule-stored products (e.g., in response to certain peptides) or cytokines, chemokines and growth factors (e.g., in response to certain microbial products).

type that can bind IgE), showing that mast cells importantly contribute to this acute, catastrophic and potentially fatal reaction. Through effects of released mast cell products on inflammation and structural cells in the affected tissues (Table 1), IgE-dependent mast cell activation can contribute to late phase reactions (that develop hours after allergen exposure) and to the features of chronic allergic inflammation (e.g., in allergic asthma).

DO MAST CELLS CONTRIBUTE TO HEALTH, OR ONLY TO DISEASE?

From an evolutionary perspective, mast cells did not develop in order to cause disease. Likely beneficial roles of mast cells include enhancing host resistance to some parasites and other pathogens and enhancing innate and acquired resistance to certain animal venoms. Mast cells also have the potential to limit the pathology associated with certain innate or acquired immune responses through the production of mediators with anti-inflammatory or immunosuppressive effects.

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10 BASOPHILS

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KEY MESSAGES

- Basophils have long been neglected in immunological studies, owing to their small numbers and phenotypic similarity to mast cells
- The finding that basophils secrete large quantities of Th2 cytokines (IL-4 and IL-13) ended the long-held view of basophils as minor relatives of mast cells with little function
- Basophils normally circulate in the blood, and are recruited to affected tissues in various allergic disorders, including allergic rhinitis, chronic urticaria, atopic dermatitis, and asthma
- Recent development of analytical tools in mouse models has identified pivotal and nonredundant roles for basophils in a variety of immune responses, including allergy

Basophils are the least abundant granulocytes, and represent less than 1% of peripheral blood leukocytes. They were first documented by Paul Ehrlich more than 100 years ago, but their functional significance remained enigmatic for a long time. Basophils share certain features with tissue-resident mast cells, including the presence of basophilic granules in the cytoplasm, the surface expression of IgE receptor (FcεRI), and the release of chemical mediators in response to various stimuli (Table 1). Therefore, they have often erroneously been considered as minor and redundant relatives or precursors of tissue-resident mast cells. Indeed, in clinical settings, basophils have been used, as surrogates of less accessible tissue mast cells, for the in vitro quantification of immediate-type response to allergens in allergic patients.

Basophils circulate in the peripheral blood, and are rarely present in peripheral tissues under homeostatic conditions, in contrast to mast cells. The half-life of circulating basophils is estimated at approximately 2 days, while mast cells survive for months in peripheral tissues. Although these differences suggest that basophils and mast cells may play distinct roles in vivo, no definitive evidence for it has been provided until recently. Basophils release preformed histamine, newly synthesized leukotriene C4, and Th2 cytokines (IL-4 and IL-13), all of which are involved in allergic reactions. Indeed, basophils have been demonstrated to infiltrate affected tissues in various allergic disorders, including allergic rhinitis, chronic urticaria, atopic dermatitis, and asthma. However, the overwhelming influx

TABLE 1

Difference between basophils and mast cells

	Basophils	Mast cells
Place of birth	bone marrow	bone marrow
Place of maturation	bone marrow	peripheral tissues
Anatomical localization	peripheral blood	peripheral tissues
Life span	short (several days)	long (weeks or months)
Proliferation capability	-	+

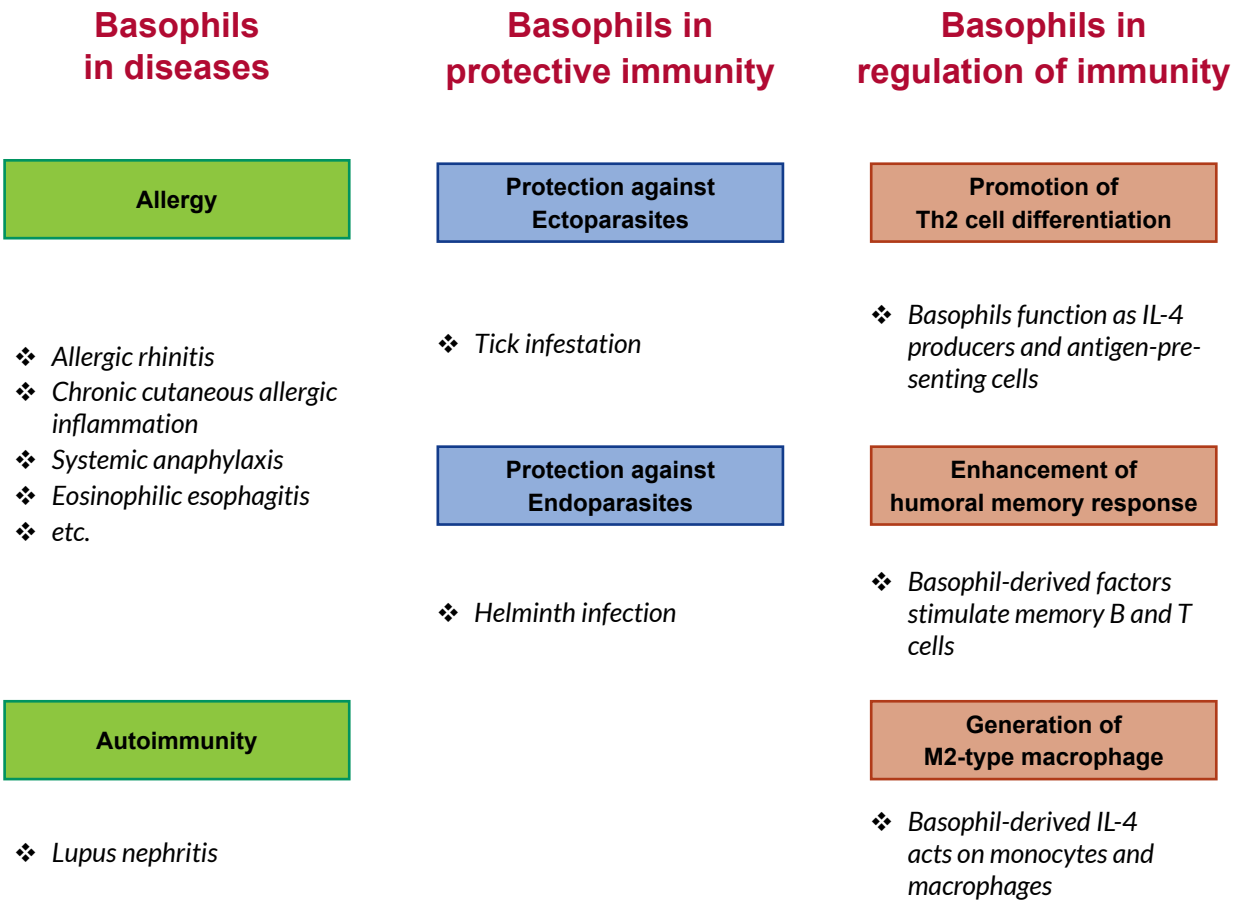

Figure 1 Previously unappreciated roles of basophils revealed by mouse studies.

of eosinophils in these responses has long overshadowed the significance of basophil infiltration and it has remained uncertain whether basophils play a crucial role or are just redundant with mast cells.

Recent development of analytical tools for basophil function in vivo, including basophil-deficient mice, has identified pivotal and nonredundant roles for basophils in a variety of immune responses in mouse models, such as allergic reactions (allergic rhinitis, chronic cutaneous allergic inflammation, systemic anaphylaxis, and eosinophilic esophagitis), autoimmunity (lupus nephritis), protective immunity against infections with parasites (ticks and intestinal helminths), and regulation of innate and acquired immunity (generation of Th2 cells and M2-type macrophages, and enhancement of humoral immunity) (Figure 1). Of note, the number of basophils recruited to affected tissues of model mice is much smaller than that of eosinophils, as observed in allergic patients, suggesting that basophils may also play key roles in the development and exacerbation of human allergic disorders in spite of their paucity. Therefore, basophils and their products could be promising targets for the treatment of allergic disorders.

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11 EOSINOPHILS

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KEY MESSAGES

- Eosinophils are multifunctional cells
- Eosinophilia in allergic diseases is largely mediated by IL-5-producing T cells
- Eosinophils can cause organ dysfunction by both cytotoxicity and fibrosis
- Specific anti-eosinophil therapies have been shown to be effective in asthma

Eosinophils are terminally differentiated granulocytic effector cells that produce and store biologically active molecules, including cytotoxic proteins, lipid mediators, chemotactic peptides, and cytokines. They are considered as multifunctional cells able to modulate both innate and adaptive immunity (Fig. 1). Eosinophils are generated in the bone marrow under the influence of eosinopoietins (IL-3, IL-5, GM-CSF), released to peripheral blood upon maturation, and mainly reside in the hematopietic and lymphatic organs, such as the bone marrow, spleen, lymph nodes, and thymus. The normal eosinophil blood count ranges from 50 to 500 x 109/L. Eosinophil numbers can increase in various inflammatory reactions, including allergic diseases. Several proposals for the classification of eosinophil-related disorders have been published. In allergic diseases, eosinophilia is largely mediated by IL-5 - producing T cells.

Clinical observations point to a potential role of eosinophils in the pathogenesis of allergic diseases. Eosinophil numbers in blood and eosinophil tissue infiltration often correlate with the severity of the disease. Therefore, therapies that reduce eosinophil numbers are usually effective in allergic diseases. Moreover, the numbers of eosinophils in sputum have been shown to predict the success of anti-eosinophil therapies in asthmatic patients. For example, tailoring of asthma treatment based on sputum eosinophils is effective in decreasing asthma exacerbations.

The exact role of eosinophils in the pathogenesis of allergic diseases is currently a topic of intensive research. In asthma, eosinophil-derived cytotoxic proteins and reactive oxygen species have been shown to damage bronchial epithelial cells, leading to a barrier defect. Eosinophils are also a source of lipid mediators, such as leukotriene C4 and platelet-activating factor, which can cause bronchoconstriction. Moreover, eosinophils can amplify T helper 2 immune reactions by the generation of cytokines. A role for eosinophils in experimental asthma has been demonstrated in eosinophil-deficient mice, which demonstrated reduced T cell recruitment and mucus production, as well as reduced bronchial hyperreactivity.

Eosinophils also play a role in tissue repair and remodeling processes. Specific anti-eosinophil treatment by using anti-IL-5 antibodies was associated with reduced fibrosis in allergic asthma and eosinophilic esophagitis. The peribronchial fibrosis was also reduced in experimental asthma induced in eosinophil-deficient mice. Therefore, eosinophils can contribute to organ dysfunction by both cytotoxicity and fibrosis.

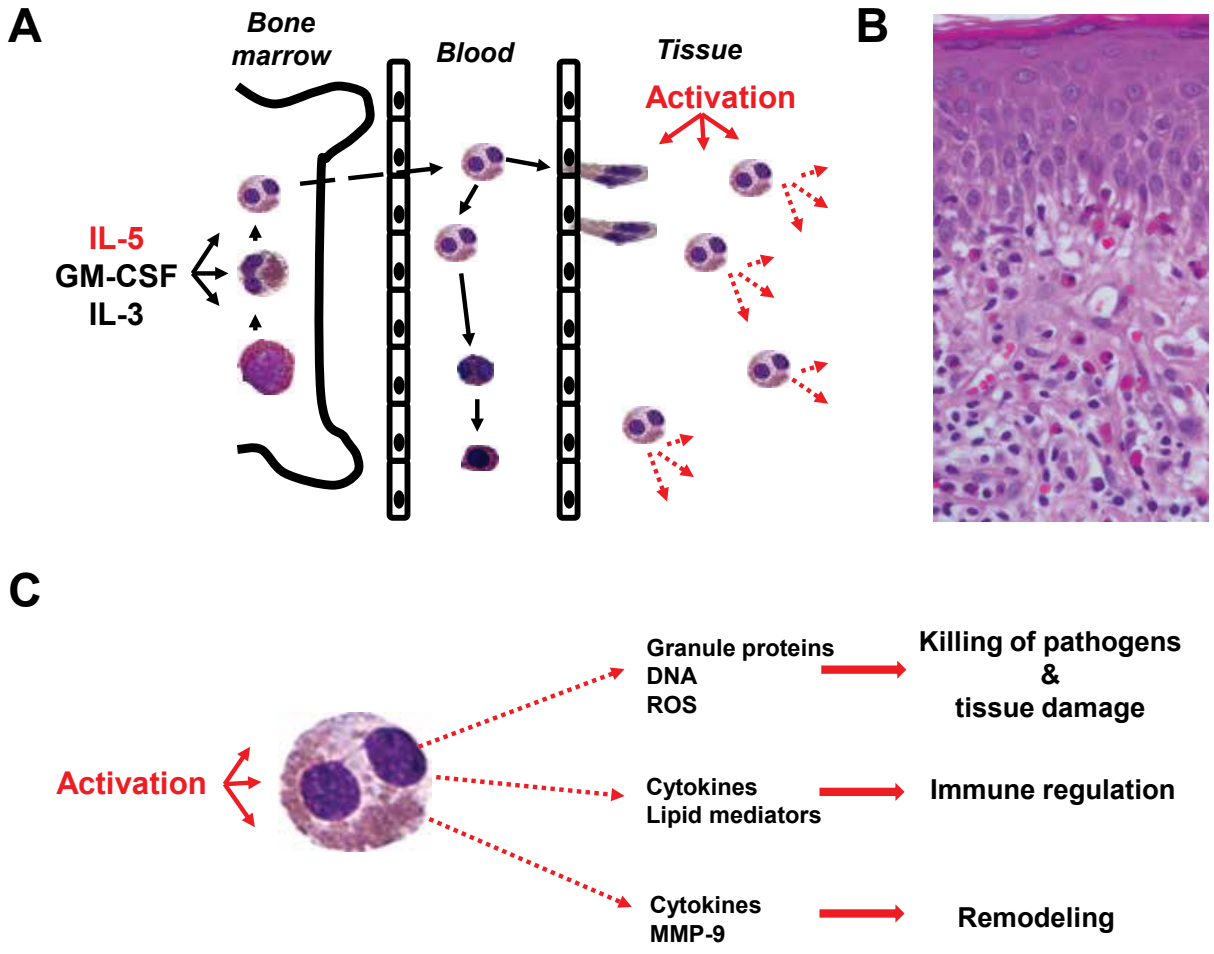

Figure 1 Tissue infiltration and role of eosinophils in diseases. (A) Eosinophils originate from multipotent and lineage-restricted hematopoietic progenitor cells. They mature in the bone marrow under the influence of eosinophilopoietic cytokines (IL-3, IL-5, and GM-CSF). Mature eosinophils are released in the peripheral blood and can infiltrate inflammatory tissues as it occurs in allergic diseases. At sites of inflammation, eosinophils are activated and their apoptosis is delayed (reviewed by Geering B, Stoeckle C, Conus S, Simon HU. Living and dying for inflammation: neutrophils, eosinophils, basophils. Trends Immunol 2013;34:398-409). Under non-inflammatory conditions, eosinophils undergo apoptosis without infiltration of organs outside the hematopoietic and lymphatic systems. (B) An example of eosinophil tissue infiltration: Eosinophil infiltration of the dermis in a patient with drug allergy. The tissue section was stained with hematoxylin and eosin (original magnification x63). (C) Eosinophils are multifunctional cells. Following activation of eosinophils, they release granule proteins and reactive oxygen species (ROS), which are able to kill pathogens, but also tissue cells possibly causing organ dysfunction. Eosinophils additionally release mitochondrial DNA, which forms together with granule proteins eosinophil extracellular traps (reviewed by Simon D, Simon HU, Yousefi S. Extracellular DNA traps in allergic, infectious, and autoimmune diseases. Allergy 2013;68:409-416). By releasing cytokines and lipid mediators, eosinophils are further involved in immune regulation and remodeling events.

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12 T CELLS

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KEY MESSAGES

- Allergy is dependent on the immunologic memory as it re-occurs regularly
- Allergic symptoms correlate with T cell activation particularly of the Th2 type
- T cells do also react to allergens in asymptomatic patients and may mediate allergen tolerance by active immune suppression

IMMUNE MEMORY - GOOD AGAINST BUGS, BAD FOR ALLERGIC AND AUTOIMMUNE DISEASES

The potency of the immune memory is assumed to be a key event in the evolution that allowed the success of larger organisms over smaller sized creatures and generated longer-lived organisms. However, the ability to remember pathogens has also its downsides.

A key feature of allergy is that the symptoms occur again every season. This is similar to the immunologic feature that memorizes determinants on pathogens or other harmless structures such as autoantigens or allergens. The inappropriate immune response caused by dysregulation of the immunologic tolerance is underlying autoimmune and allergic diseases.

Both memory and immune tolerance are mediated by T lymphocytes, which recognize immunogenic structures by the T-cell receptor (TCR). This receptor is characterized by a very high variability that is generated by multiple gene-segment cassettes that are alternatively rearranged to generate a final gene product. Further variation is introduced by a flexible fusion process that increases variability and, thus, an extended repertoire of TCRs that cover most determinants of our environment is generated. Apart from the sophisticated structure of TCRs, the activation and differentiation of these cells is integrating multiple signals from the tissue, the immune system and the external environment. This integration process involves antigen-presenting cells (APC) that need to digest the environmental allergen/antigen and present it in a molecule with similar high diversity as the TCR. Major histocompatibility complexes, (MHC) bring the digested peptides to the surface of the APC and also deliver additional signals that are essential for the activation or deactivation of T cells. The successful activated T cell will divide and after the termination of an immune response some cells (memory cells) will remain. These memory cells are able to quickly expand and reproduce an immune response that has been proven to be successful. It is anticipated that the generation of memory cells is underlying successful immunizations (vaccination) against infectious agents. Hyposensitisation by allergen-specific immunotherapy (AIT) may also be governed by memory populations.

DECISION MAKING IN THE IMMUNE SYSTEM

The decision making process is subject of immunology research and has the intention to solve the “black box” of immune tolerance mechanisms. The goals are to prevent the loss of immune tolerance by means of public health initiatives (e.g. pollution control, dietary advices etc.), to increase effectiveness of specific immunotherapy and similar vaccination

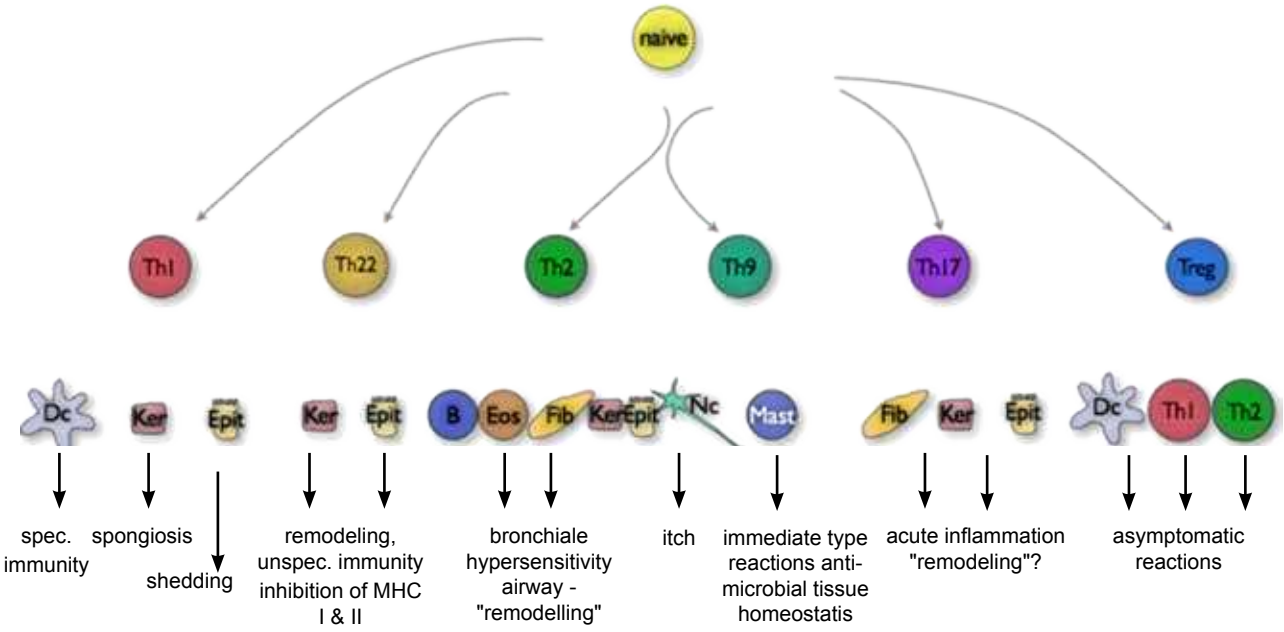

Figure 1 Different T cell phenotypes arise from naïve (resting, not antigen-experienced T cells) upon activation by antigen-presenting cells and by decision cytokines (not shown). The figure highlights a variety of responding cells both of the immune system as well as from non-immune (mesenteric) origin.

strategies and to develop new therapies that prevent severe tissue damage as it occurs in the gut, skin and airways. The decision of the immune system is reflected by the T lymphocyte activity, mainly by their secreted mediators, interleukins (IL). Interleukins are typically of the "Th2"-type including IL-4, IL-5 and IL-13, whereas autoimmune or pathogen-trigged T cells usually express "Th1- or Th17-type" IL's and interferons (IFN) such as IFN-γ or IL-17. IL-4 produced by T cells is essential for the production of IgE, the diagnostic key parameter in the detection of allergies. The interleukins have various functions and are characterizing the regulatory impact of T cells on other immune cells and on tissue cells. The exploration of T cell mediated signals on tissue cells is just beginning and it is already revealed that T cells can directly mediate tissue pathology such as epithelial damage or collagen deposition (Figure 1).

TERMINATING IMMUNE RESPONSES

This holds particularly true for the immune system. T regulatory (Treg) cells represent a key discovery that falls into this category, as they are actively suppressing other immune cells particularly Th1, -2 and-17 cells. In fact, healthy individuals are showing immune activation in vitro, suggesting that mechanisms exist that keep these processes under asymptomatic control. Novel immune regulatory T cell phenotypes are hypothesized to mediate anti-inflammatory signals also to tissue cells. AIT is assumed to generate Treg cells and future research and novel pharmaceutical strategies are aiming to reinforce these mechanisms in order to re-construct immune tolerance under minimal influence on anti-pathogen responses.

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13 B CELLS

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KEY MESSAGES

- By their production of allergen-specific IgE antibodies B cells contribute to the pathophysiology of a wide range of allergic diseases
- $CD4^+$ Th2 cells that produce IL-4 and express CD40L orchestrate the IgE-switch and differentiation of B cells
- The recently described B regulatory cells inhibit over-activated immune responses
- Elucidating mechanisms regulating the bifurcation of B cell responses into B regulatory versus IgE-producing cells holds promise for therapeutic interventions

B cells are crucial in allergic diseases by virtue of their production of allergen-specific IgE antibodies, which play a key role in instigating immediate hypersensitivity reactions and contribute to the pathophysiology of a wide range of allergic diseases ranging from asthma, atopic dermatitis, food and drug allergy, amongst others. IgE-production by B cells entails class-switch recombination at the immunoglobulin heavy chain locus into the IgE heavy chain (Cε). $CD4^+$ Th2 cells that produce IL-4 and express CD40L orchestrate the differentiation of IgE-switched B cells. It has been suggested that there are two pathways for IgE production after secondary exposure to antigen.

The first involves the differentiation of IgE-switched plasma cells from $IgG1^+$ precursors by sequential switching from Cγ1 to Cε, leading to the production of high affinity IgE antibodies by somatic hypermutation (affinity maturation). The second pathway involves the direct differentiation of IgE^+ memory B cells generated during the primary immune response into plasma cells, leading to a robust recall IgE antibody response. The relative contribution of each pathway to the generation of disease-promoting pathogenic IgE antibodies remains to be established (Figure 1).

The highly variable correlation between the levels of allergen-specific IgE antibodies and susceptibility to anaphylaxis indicates that other factors, such as IgG antibodies, have profound influences on IgE-mediated responses. Immunotherapy to aeroallergens has been shown to stimulate the production of allergen-specific IgG1 and IgG4 antibodies, that protect against disease by inhibiting allergen interaction with FcεRI-bound IgE on mast cells and basophils, thus preventing their degranulation.

Recently, much attention has been given to regulatory B (Breg) cells that inhibit over-activated immune responses. Several groups have proposed that a reduction in Breg cells worsens symptoms of allergic disease such as contact hypersensitivity and anaphylaxis. Breg cells are characterized by their production of the negative regulatory cytokines, IL-10 and TGF-β. An increased number of IL-10-producing B cells has been found in *S. mansoni* worm infection and the *in vivo* transfer of these cells prevents recipient mice from anaphylaxis. Breg cells proliferate when stimulated with the milk antigen casein in milk tolerant but not in milk allergic patients. Akdis and colleagues recently found increased suppressive $IL10^+$ Breg

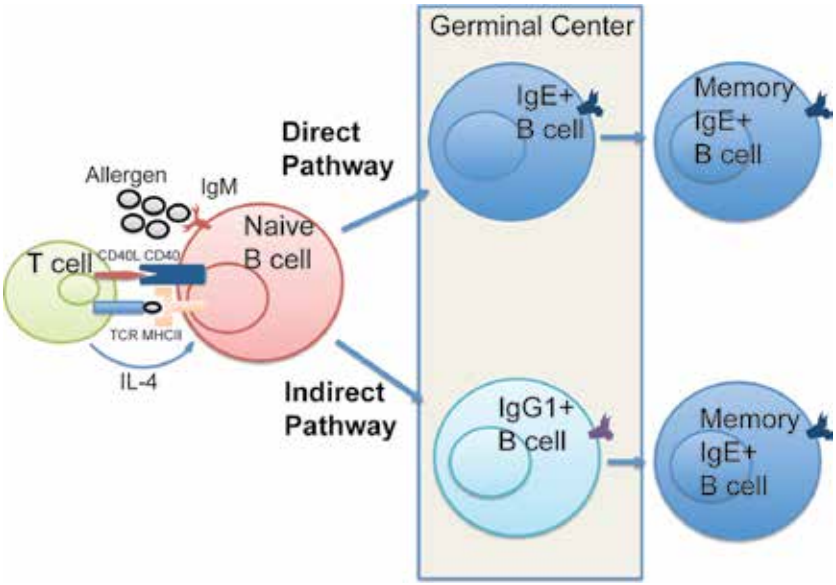

Figure 1 Pathways for the generation of memory B cells. The interaction of Th2 cells with allergen-specific B cells may lead to switching into either IgE+ or IgG1+ memory B cells. The former would differentiate directly to IgE+ plasma cells upon recall responses, while the latter would first undergo switching from Cγ1 to Cε before further differentiating into plasma cells.

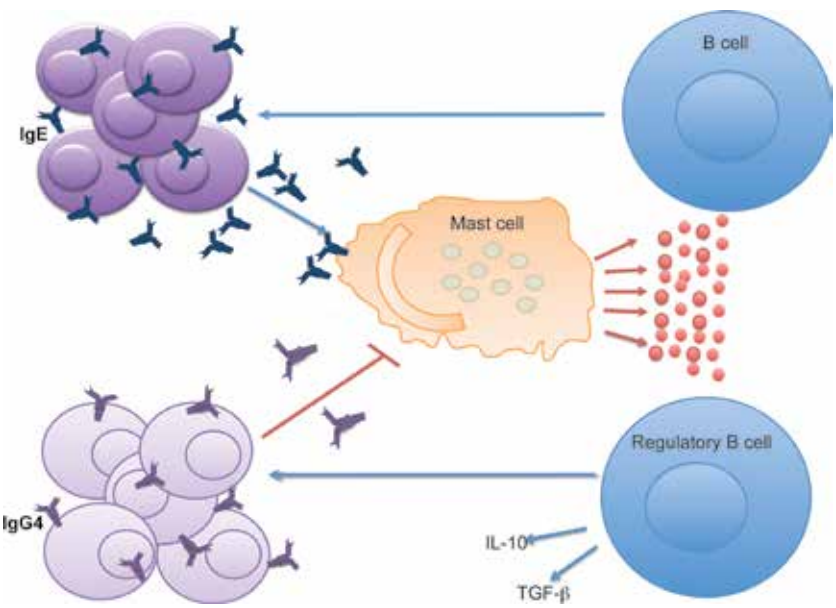

Figure 2 Opposing actions of IgE and IgG4 in allergic responses. Allergen-specific IgG4, generated during immunotherapy, blocks the interaction of allergens to IgE and abrogates IgE-dependent effector responses. Regulatory B cells may promote tolerance by differentiating into allergen-specific IgG4-producing plasma cells.

cells in non-allergic beekeepers undergoing allergen-specific immunotherapy and high-dose venom exposure. They revealed that Breg cells are specifically developing into IgG4-producing plasma cells (Figure 2). Thus, elucidating mechanisms regulating the bifurcation of B cell responses into Breg versus IgE producing cells holds promise for therapeutic interventions.

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14 IMMUNOGLOBULIN E AND OTHER ANTIBODIES IN ALLERGY

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KEY MESSAGES

- Antibodies of the IgE class are central to the allergic response.
- IgE antibodies are synthesized and secreted by allergen-specific B cells that have undergone heavy-chain class switching to IgE and differentiated into IgE-secreting plasma cells
- IgE binds to FcεRI on mast cells and antigen (in this case allergen)-presenting cells to sensitize the cells for allergen activation
- The immediate symptoms of allergy are caused by the release of potent physiological mediators produced by the allergen-activated mast cells, while the activated antigen-presenting cells indirectly induce new allergen-specific B cells to produce more IgE
- Allergen immunotherapy can generate allergen-specific antibodies of IgG and IgA classes to compete with IgE for allergens

Immunoglobulin E (IgE) is one of five antibody classes, IgM, IgD, IgG, IgA and IgE, in mammals (Figure 1). There are four subclasses of IgG (IgG1-4) and two of IgA (IgA1, IgA2), making a total of 9 nine different classes including the subclasses in humans.

Every person can produce an antibody to recognize virtually any potential antigen by a combination of mechanisms. The initial repertoire of IgMs generated in the bone marrow by "V(D)J" gene recombination and junctional nucleotide variation is highly diverse and is further adapted by antigen stimulation of the B cells in the immune response. This results in cell proliferation and the formation of germinal centers in lymphoid tissues, where they undergo two processes: somatic hypermutation (SHM) and class switch recombination (CSR). SHM introduces point mutations in the antigen-binding sites, which may increase or decrease affinity for antigen resulting in selection of high-affinity mutants that compete for antigen in a process called affinity maturation. CSR replaces the constant region of the heavy-chain with one of another class encoded in a tandem array downstream from the VDJ sequence in the expressed immunoglobulin gene (Figure 2). This changes the antibody class and the way it is able to engage different effector cells in the immune response. Germinal center reactions may also occur in the target organs of allergy.

Antibodies of the IgE class are central to the allergic response (Figure 3). They are synthesized and secreted by IgE-expressing B cells that have differentiated into IgE-secreting plasma cells. IgEs bind to mast cells and antigen-presenting cells bearing the high-affinity IgE receptor, FcεRI, to sensitize the cells for allergen activation. Allergen-activated mast cells release the physiologically potent molecules that cause the symptoms of allergy. The activated antigen-presenting cells stimulate T helper 2 (Th2) cells, which in turn induce the production of more allergen-specific antibodies in a positive feedback loop primed by allergen.

Antibodies of the same or cross-reacting specificity, but another antibody class can compete with IgE for antigen binding to prevent or suppress the allergic response. This may occur in specific allergen immunotherapy, which stimulates a modified Th2 response, causing a massive up-regulation of IgG4 and IgA2. Some of these antibodies may recognize the allergen and

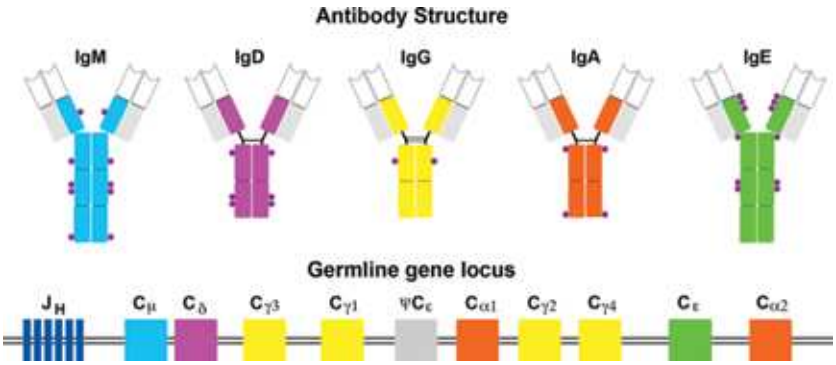

Figure 1 All five antibody classes have the same basic "immunoglobulin" structure with two heavy- and two light-chains, each with variable-regions (white) containing the antigen-combining site and class-specific constant-regions shown in different colors. The distinctive ε constant region of the IgE heavy-chain is shown in green. Carbohydrates attached to the protein are depicted as small purple circles. The different constant-regions are encoded in a tandem array in the germ line immunoglobulin heavy-chain gene locus on human chromosome 14, downstream from the heavy-chain variable-region of the expressed heavy-chain gene.

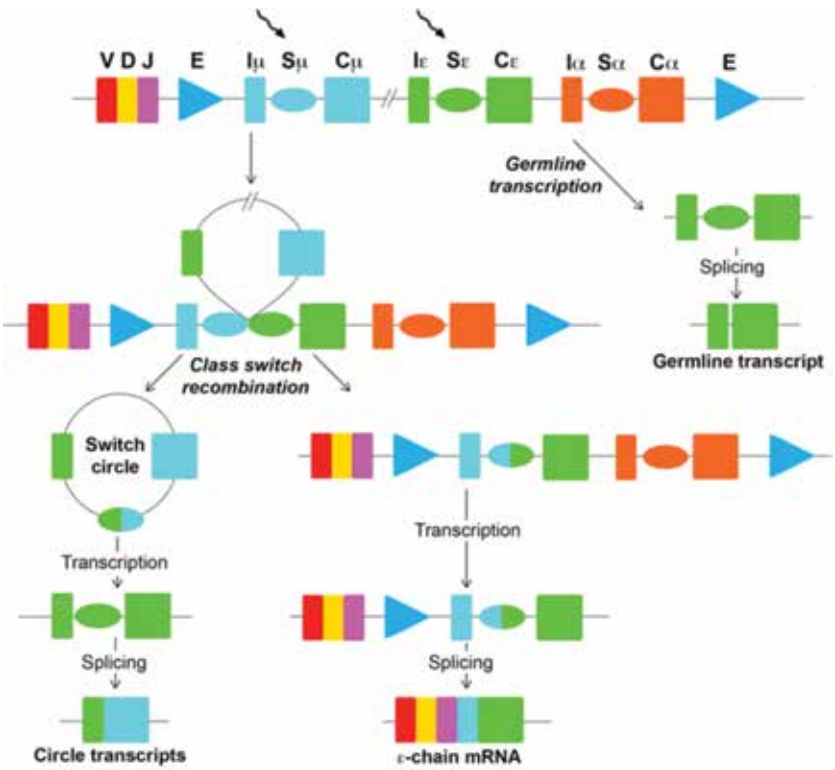

Figure 2 Class switch recombination is required to express IgE. The immunoglobulin heavy-chain locus contains the rearranged variable (VDJ) region linked to a transcriptional enhancer (E) and a series of three elements required for expression of the complete heavy-chain, an "intervening" exon (I), a switch region (S) and a constant region (C). During class switch recombination the VDJ, I and proximal part of S are recombined with the distal part of S within another germ line gene cassette (I, S, and C distinguished by Greek letters corresponding to the newly expressed antibody class). The intervening sequence is deleted and the ends join to form a circle. Prior to recombination, specific cytokines stimulate germ line gene transcription from the I exon promoters of the two genes that subsequently undergo recombination. The germ line gene transcript corresponding to the gene to be expressed helps to instigate the subsequent recombination. The I exon promoter in the switch circle, now attached to the previously expressed gene, remains transiently active, producing a circle transcript whose sequences can be used to identify the genes that recombined. The new immunoglobulin gene in the shortened chromosome is expressed from the VDJ promoter, leading to the synthesis of the immunoglobulin heavy-chain mRNA and protein. The light-chain is unchanged after heavy-chain recombination.

compete with IgE. It is thought that immune deviation to IgG4 and IgA2 allergen specificities may contribute to the success of specific allergen immunotherapy (Figure 4).

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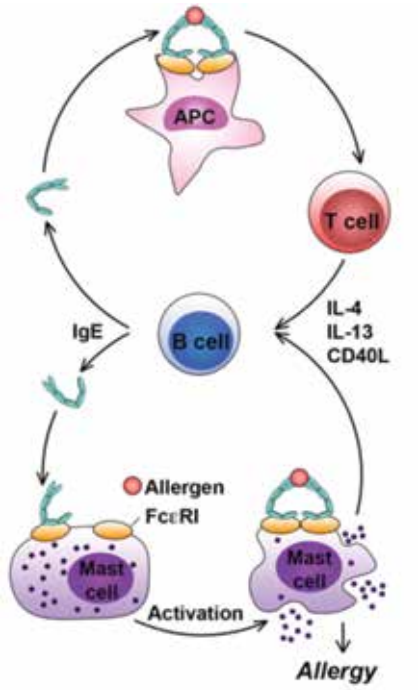

Figure 3 IgE binds very tightly to mast cells and antigen-presenting cells through its high-affinity receptor, FcεRI. Specific allergen crosslinking of the IgE-receptor complex on mast cells induces cell degranulation with the release of mediators leading to the allergic response and also the production of IL-4 and IL-13 and expression of CD40L by the antigen-presenting cells and mast cells. These cytokines lead to B cell proliferation and further switching to IgE in B cells expressing other isotypes in a positive feedback loop, resulting the generation of even more IgE.

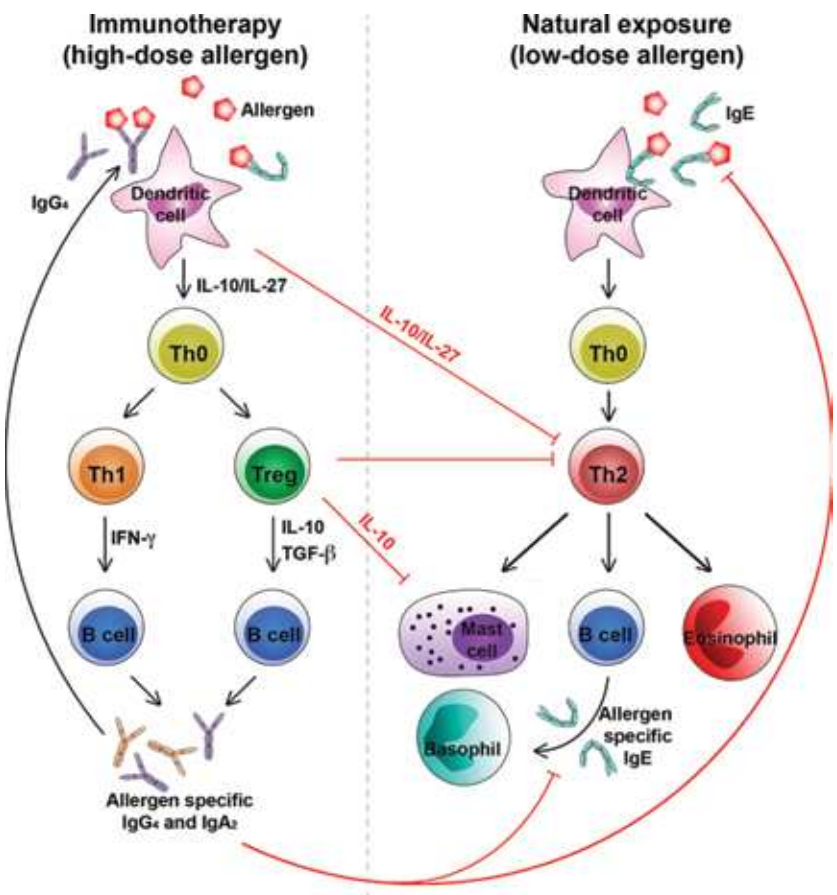

Figure 4 Natural exposure to allergens may induce allergen-specific IgE production in sensitive individuals by stimulation of antigen-presenting cells in a T helper 2 (Th2) immune response. This IgE sensitizes effector cells (mast cells, basophils and eosinophils) and the generation of allergen-specific IgE by B cells. Exposure to high-doses of allergens through immunotherapy induces IL-10/IL27 release from dendritic cells leading to suppression of the Th2 by deviation of T cell differentiation into the T helper 1 cell and T regulatory (Treg) cell pathways. The resultant cytokines, IFN-γ IL-12, IL-10 and TGF-β lead to the generation of allergen-specific IgG4 and IgA2 antibodies that compete with IgE for allergens.

15 ROLE OF SUPERANTIGENS IN ALLERGIC DISEASES

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KEY MESSAGES

- *Staphylococcus aureus* is a major trigger of atopic dermatitis and may contribute to severity of rhinosinusitis and asthma
- *S. aureus* exacerbates allergic diseases by secreting virulence factors such as superantigens and alpha toxin
- Staphylococcal virulence factors alter host responses to allergens and microbes
- Th2 skin immune responses and filaggrin deficiency increases the propensity of atopic skin to become colonized and infected with *S. aureus*

Atopic dermatitis (AD) is the most common chronic skin disease in the general population. It often presents during early childhood and is the prelude to development of food allergy, asthma and allergic rhinitis. A majority of AD patients have a systemic and skin directed Th2 immune response leading to allergen sensitization and increased skin colonization with *Staphylococcus aureus* (*S. aureus*). These patients also have a defect in the terminal differentiation of their skin keratinocytes leading to reduced expression of skin barrier proteins such as filaggrin, and decreased expression of antimicrobial peptides needed for skin host defense against invading bacteria and viruses. Reduced barrier function is due to a combination of gene mutations encoding skin barrier proteins such as filaggrin with the downregulation of epithelial differentiation protein levels induced by Th2-type cytokines and IL-22. Loss of filaggrin has been linked to enhanced allergen penetration into the skin, increased *S. aureus* growth and *S. aureus* infection (Figure 1). *Staphylococcus aureus* triggers and maintains skin inflammation in AD via the production of virulence factors, such as superantigens and alpha toxin (Figure 2).

Figure 1 Child with atopic dermatitis superinfected with superantigen secreting *Staphylococcus aureus. (Reprinted from J Allergy Clin Immunol, 125/1, Boguniewicz M, Leung DY. Recent insights into atopic dermatitis and implications for management of infectious complications, 4-13, Copyright 2010, with permission from Elsevier.)*

Superantigens are potent polyclonal T cell activators that also stimulates cytokine release from antigen-presenting cells (Figure 3). Evidence supporting a role for superantigens in AD include the observation that most AD patients make IgE antibodies directed against superantigens found on their skin and the presence of these IgE antibodies to superantigens correlate with skin disease severity. Basophils and skin mast cells from patients with anti-superantigen IgE release histamine on exposure to superantigens, but not in response to superantigens to which they have no specific IgE. Importantly, the superantigen, staphylococcal enterotoxin B (SEB), can induce eczematoid skin changes when applied to the skin. After stimulation by SEB, T regulatory cells lose their immuno-

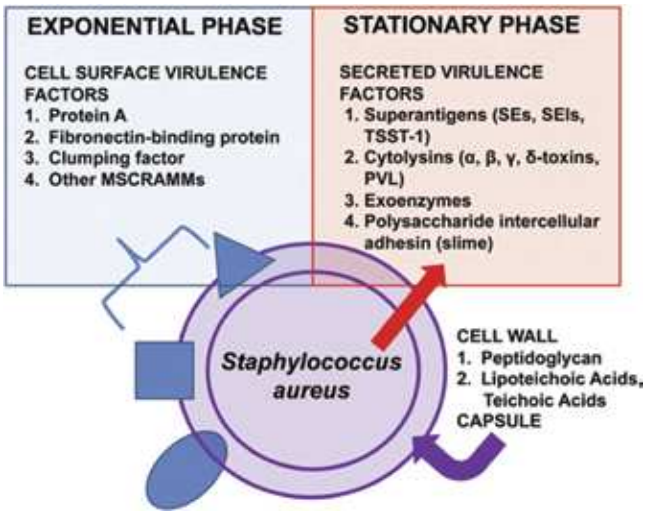

Figure 2 Virulence factor production by *S. aureus (Reprinted from J Allergy Clin Immunol, 125/1, Schlievert PM, Strandberg KL, Lin YC, Peterson ML, Leung DYM. Secreted virulence factor comparison between methicillin-resistant and methicillin-sensitive Staphylococcus aureus, and its relevance to atopic dermatitis, 39-49, Copyright 2010, with permission from Elsevier.)*

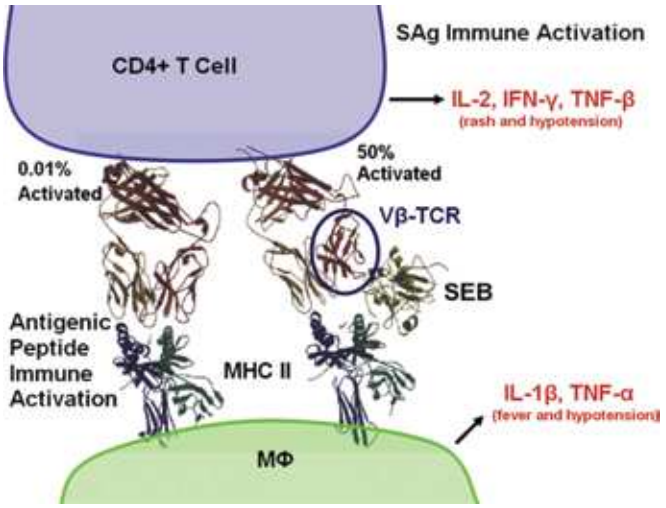

Figure 3 Model comparing activation of CD4+ T cells and macrophages by the superantigen, SEB, compared with antigenic peptide activation of the same cells. In comparison to peptide activation, SEB causes polyclonal T cell stimulation. *(Reprinted from J Allergy Clin Immunol, 125/1, Schlievert PM, Strandberg KL, Lin YC, Peterson ML, Leung DYM. Secreted virulence factor comparison between methicillin-resistant and methicillin-sensitive Staphylococcus aureus, and its relevance to atopic dermatitis, 39-49, Copyright 2010, with permission from Elsevier.)*

suppressive activity, suggesting a novel mechanism by which superantigens could augment T-cell activation and skin inflammation in patients with AD. Superantigens also selectively induce T cells to become corticosteroid resistant and to secrete IL-31, a highly pruritogenic cytokine that induces eczema in animal models.

Treatment of AD patients should focus on skin barrier repair with reduction of skin inflammation. AD patients with S. aureus infection should receive antibiotics as this may reduce the severity of their skin disease. Together, these observations fulfill Koch's postulates and support a role for staphylococcal superantigens in AD.

There is also increasing data suggesting that in certain clinical situations, *S. aureus* may contribute to severity of rhinosinusitis and asthma, by augmenting the airway inflammation and promoting polyclonal local IgE formation, and by inducing corticosteroid resistance.

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16 CYTOKINES IN ALLERGY

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KEY MESSAGES

- Cytokines act as messengers of the immune system with other cells of the body
- Various groups of cytokines are responsible for the sensitisation to an allergen and for eliciting the allergic inflammation.
- There are sensing cytokines, T cell instructing cytokines, effector cytokines, resolving cytokines and chemokines
- The integrated actions of the cytokines in development, elicitation and eventually resolving the inflammation is called the *cytokine network of allergy*

Cytokines are soluble proteins or peptides that act as the hormones - messengers - of the immune system and between other cells of the body. They confer cell-to-cell communication which may take place between adjacent cells (*juxtacrine*) or cells in different organs of the body (*para-* or *endocrine*). A cytokine signal is delivered via a receptor on the surface of a cell, and since different cells may express the same receptor, a cytokine can have several functions (*pleiotropy*) depending on the target cell. Also a target cell may have receptors for several similar cytokines allowing for *redundancy*.

There are more than 100 described cytokines and their names are not easy to cope with, since no unified nomenclature exists. Some are named after where they were first found and/or their function, such as thymic stromal lymphopoietin (TSLP), others after the first function identified, like Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), and some may even have several names given to them by different research groups. An attempt to unify the nomenclature has been made by the word *interleukin* - meaning messengers between white blood cells - followed by a number, but more and similar molecules have been discovered, so instead of just interleukin-1 (IL-1), we now have IL-1α, IL-1β and IL-1RA (= Interleukin 1 Receptor Antagonist).

Various groups of cytokines are responsible for the different phases of the allergic *sensitization* (building up the allergic immune response) and *elicitation* (reactions upon exposure to an allergen):

The sensing cytokines: IL-33, IL-25, TSLP. These are released from the epithelial cells of the mucous membranes and signals to the allergen-presenting dendritic cells to take up incoming allergens and bring them to the lymph nodes.

The T-cell instructing cytokines will instruct undifferentiated T helper (CD4+) cell to develop into different kinds of cells, each of them equipped for different kinds of immune response: IL-12 and γ-interferon will produce T helper cells type 1 (Th1) that helps fighting bacteria and viruses, IL-4 leads to Th2 cells which fights large multicellular parasites like worms, but unfortunately also create the allergic immune response. Other Th-cell types such as Th17 (believed to be active in fighting bacterial or fungal infections, but unfortunately also involved in autoimmune diseases), and T regulatory (dampening the inflammation) also exists.

T-cell effector cytokines in allergy are the cytokines by which Th-cells exerts their action: Th2 cells release IL-4 and IL-13 which in-

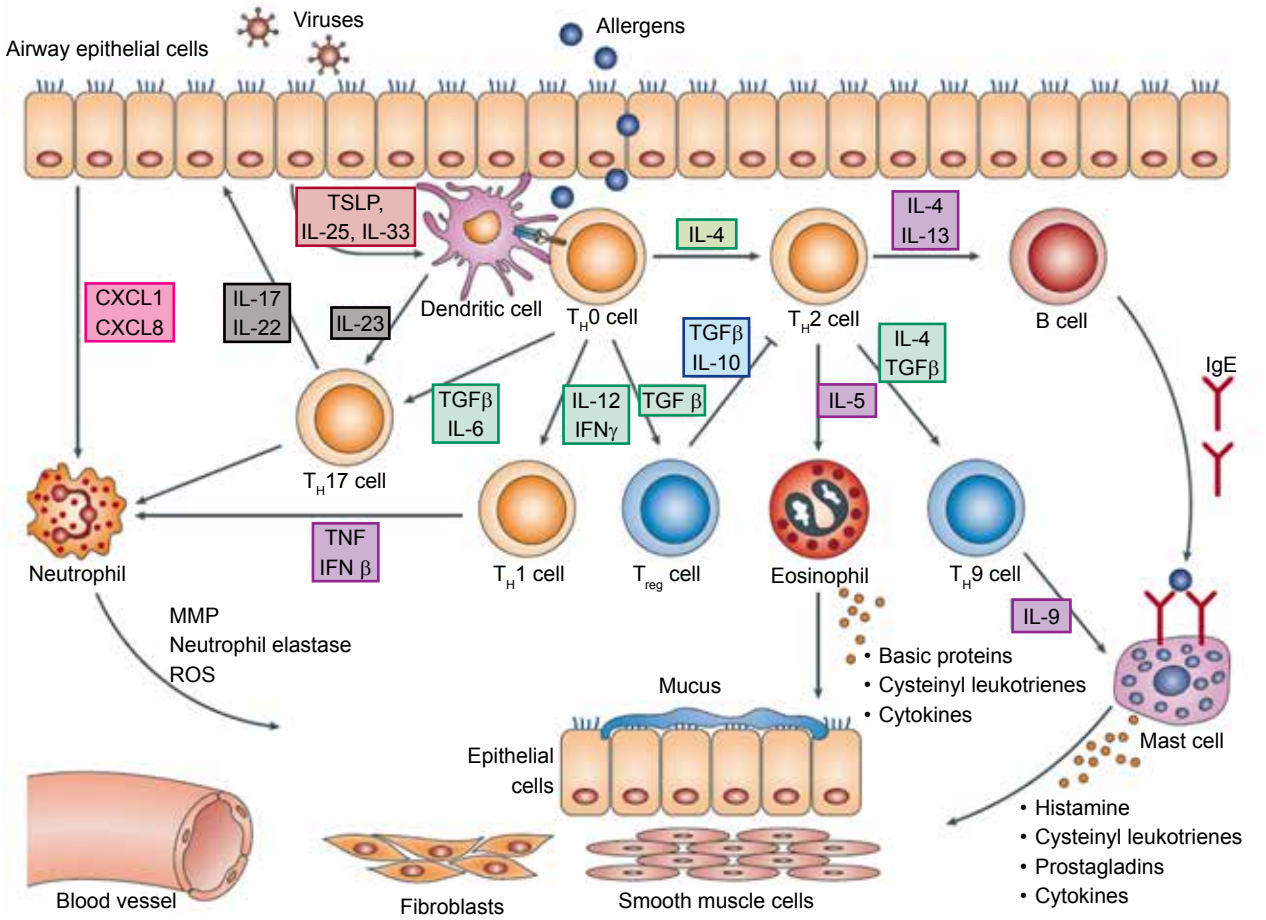

Figure 1 The complex interplay of cytokines in allergic inflammation: red - sensing cytokines; green - T-cell instructing cytokines; violet - T-cell effector cytokines; blue - Resolving cytokines; pink - Chemokines.

structs B-cells to produce the allergy antibody IgE, IL-5 that stimulates the bone marrow to form the eosinophilic granulocyte, and IL-9 that together with IL-13 creates the allergic inflammation e.g. in the lung as is the case in asthma.

The resolving cytokines such as IL-10 and Transforming Growth Factor (TGF-β) comprise a small but important group of cytokines that down-regulates the allergic inflammation, restoring the homeostasis of the immune system.

Chemokines is a special group of cytokines that attract leukocytes to the site of inflammation, and the immune system uses these to move leukocytes in the tissues, when they have left the bloodstream.

The integrated actions of the cytokines in development, elicitation and eventually resolving the inflammation is called *the cytokine network of allergy*. Since several of these cytokines play a profound role in allergy, many attempts are being made to use this therapeutically by the so-called biological therapeutics where cytokine actions are antagonized.

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17 CELL MIGRATION AND CHEMOKINES

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KEY MESSAGES

- Cell migration in the immune system is a highly regulated, multi-step process involving adhesion molecules, chemotactic factors and their receptors and is necessary for the homeostatic immune surveillance as well as for the coordinated recruitment of inflammatory cells at sites of inflammation
- Chemokines represent a superfamily of small proteins that regulate immune cell trafficking and the recruitment and activation of specific leukocyte cell types to sites of inflammation
- Chemokines are divided in four subclasses – CC, CXC, CX3C and C – and activate cell targets through class-specific seven-transmembrane chemokine receptors
- Dysregulation of the chemokine system plays a crucial role in chronic inflammatory diseases, metabolic disorders, cancer and aging
- Antagonism of chemokine receptors has so far shown partial success as therapeutic strategy, and is now assisted by research toward more specific downstream regulatory pathways modulating the chemokine network

The immune system relies on a tightly regulated migration process for the ordered compartmentalization of immune cells within the lymphoid organs, for implementation of the homeostatic immune surveillance as well as for an appropriate response to environmental insults through innate and adaptive effector responses. Circulating leukocytes and tissue-dwelling immune cells proceed from hematopoietic to vascular compartments and into tissue sites through receptor-mediated, multi-step processes involving many classes of trafficking molecules, including adhesion molecules (selectins and integrins) with their counterligands and chemoattractants, either lipid-derived or belonging to the chemokine superfamily. It is the combinatorial nature of the diverse patterns of expression and activation of these molecules and their receptors on immune and structural cells, together with their modulation in response to environmental clues, as in case of inflammatory or tumorigenic settings, that ultimately provides a high level of specificity in cellular trafficking.

Chemokines constitute a superfamily of small polypeptides, whose first identified member, CXCL8, was initially characterized by its potent and specific leukocyte chemoattractant activity – hence the name, derived from 'chemotactic cytokines'. Chemokines are divided into the CXC, CC, CX3C and C subfamilies based on the number and spacing of conserved cysteine residues. They bind to the seven-transmembrane, G-protein coupled receptors that are specific for each subclass, with multiple members sharing the same receptor (Table 1). The ensuing signaling involves multiple and diverse pathways that are highly receptor-, cell type- and context-specific and produce diverse functional outcomes. Among these, the control of immune cell trafficking in homeostasis and the regulation of leukocyte recruitment, phenotype and activation in innate and adaptive immune responses remains a defining and pivotal function of

TABLE 1

Nomenclature of Chemokine Families and Paired Receptors

Standard name	Chromo-some	Human ligand	Chemokine receptor(s)
CXC-chemokines			
CXCL1	4q21.1	GROα/MGSAα	CXCR2>CXCR1
CXCL2	4q21.1	GROβ/MIP-2α	CXCR2
CXCL3	4q21.1	GROβ/MIP-2β	CXCR2
CXCL4	4q21.1	Platelet Factor-4	CXCR3 (CD183)
CXCL4L1	4q12-q21	PF4V1	CXCR3 (CD183)
CXCL5	4q21.1	ENA-78	CXCR2
CXCL6	4q21.1	GCP-2	CXCR1,CXCR2
CXCL7	4q21.1	NAP-2	CXCR2
CXCL8	4q21.1	IL-8	CXCR1,CXCR2
CXCL9	4q21.1	MIG	CXCR3 (CD183)
CXCL10	4q21.1	IP-10	CXCR3 (CD183)
CXCL11	4q21.1	I-TAC	CXCR3 (CD183)
CXCL12	10q11.21	SDF-1α/β	CXCR4 (CD184)
CXCL13	4q21.1	BCLC	CXCR5
CXCL14	5q31.1	BRAK	CXCR4 (CD184)
CXCL15*			
CXCL16	17p13	SR-PSOX	CXCR6
CXCL17	19q13.2	DMC	Unknown
C-chemokines			
XCL1	1q24.2	Lymphotactin/α	XCR1
XCL2	1q24.2	Lymphotactin/β	XCR1
CX_3C-chemokines			
CX_3CL1	16q13	Fractalkine	CX_3CR1
CC-chemokines			
CCL1	17q11.2	I-309	CCR3
CCL2	17q11.2	MCP-1	CCR2
CCL3	17q12	MIP-1α	CCR1, CCR5 (CD195)
CCL3L1	17q21.1	LD78β	CCR1, CCR5 (CD195)
CCL3L3	17q21.1	LD78β	CCR1, CCR5 (CD195)
CCL4	17q12	MIP-1β	CCR5 (CD195)
CCL4L1	17q12	LAG-1	CCR5 (CD195)
CCL4L2	17q12	CCL4L	CCR5 (CD195)
CCL5	17q12	RANTES	CCR1, CCR3, CCR5 (CD195)
CCL6*			
CCL7	17q11.2	MCP-3	CCR1, CCR2, CCR3
CCL8	17q11.2	MCP-2	CCR3, CCR5 (CD195)
CCL9*			
CCL10*			
CCL11	17q11.2	Eotaxin	CCR3
CCL12*			
CCL13	17q11.2	MCP-4	CCR2, CCR3
CCL14	17q12	HCC-1	CCR1, CCR5 (CD195)
CCL15	17q12	HCC-2	CCR1, CCR3
CCL16	17q12	HCC-4	CCR1, CCR2
CCL17	16q13	TARC	CCR4
CCL18	17q12	PARC	Unknown
CCL19	9p13.3	ELC	CCR7 (CD197)
CCL20	2q36.3	MIP-3α, LARC	CCR6
CCL21	9p13.3	SLC	CCR7 (CD197)
CCL22	16q13	MDC	CCR4
CCL23	17q12	MPIF-1	CCR1
CCL24	7q11.23	Eotaxin-2	CCR3
CCL25	19p13.3	TECK	CCR9
CCL26	7q11.23	Eotaxin-3	CCR3
CCL27	9p13.3	CTACK	CCR10
CCL28	5p12	MEC	CCR3/CCR10

**No human ortholog described*

Modified from Bachelerie et al., Pharmacol. Rev. 66: 1-79, 2014, with update on Pubmed Library and Genebank.

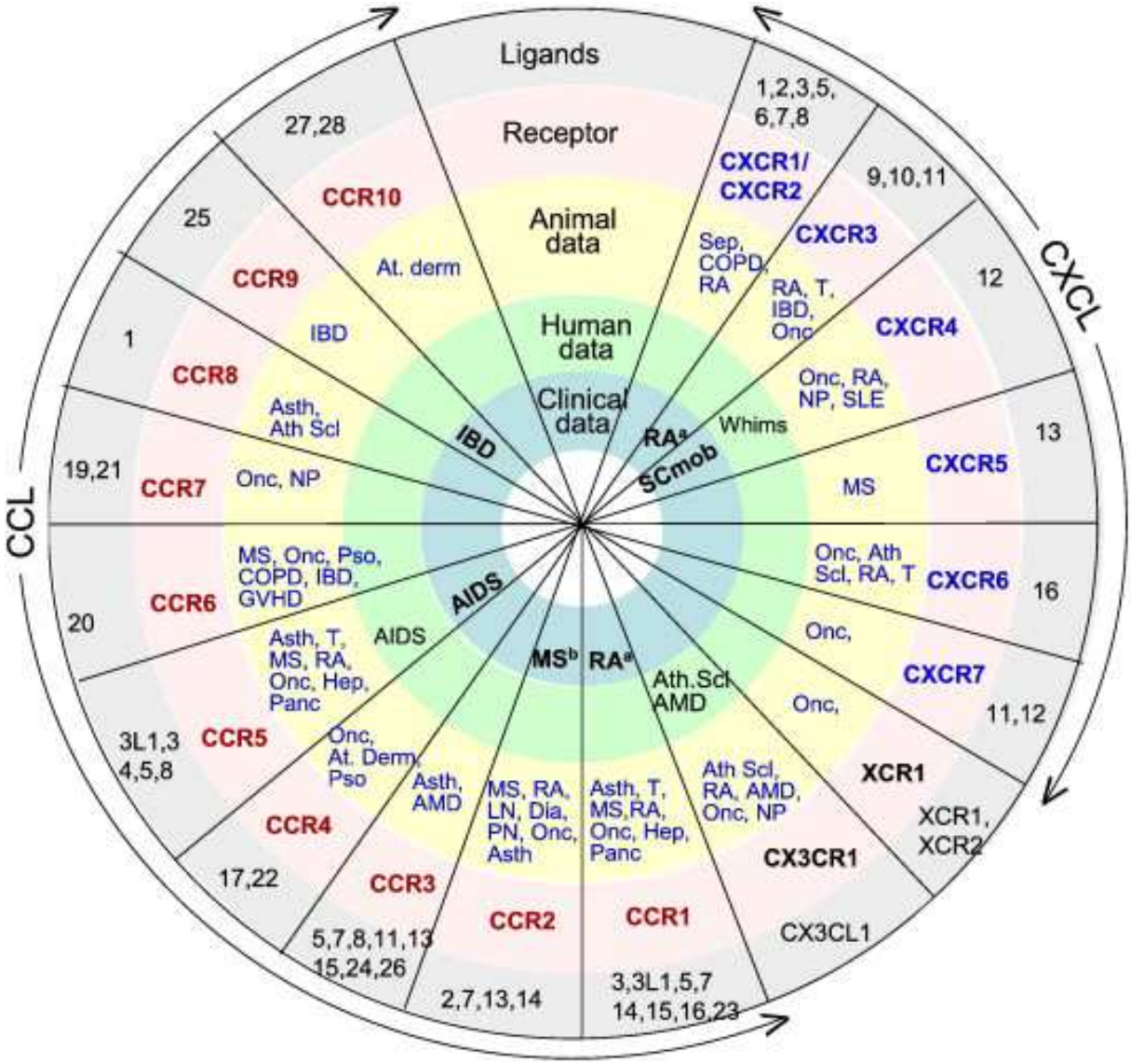

Figure 1 . The association of CC and CXC chemokines (CCL and CXCL indicated by outer arrows, member numbers listed in the outer gray circle) and their receptors (listed in pink circle below) to a selection of diseases, gained from animal models and from data obtained in human samples and in clinical trials. Abbreviations: Sep, Sepsis; RA, Rheumatoid arthritis; T, Transplant; IBD, Inflammatory Bowel Disease; Onc, Oncology; SLE, Systemic Lupus; MS, Multiple Sclerosis; Ath Scl, Atherosclerosis; COPD: Chronic Obstructive Pulmonary Disease; AMD, Acute macular degeneration; NP, Neuropathic pain; Asth, Asthma; At. Derm, Atopic dermatitis; Hep, Hepatitis; Panc, Pancreatitis; Pso, Psoriasis; GVHD, Graft vs Host disease. (*Reprinted with permission from Garin and Proudfoot, Exp. Cell. Res. 317: 602-612, 2011.*)

the chemokine superfamily. The key role of chemokines in chronic inflammatory diseases is now firmly established (Figure 1). In these contexts, the CXC and CC subclasses, though with overlaps, segregate their control over different cell types, with CXC members acting on effector functions relevant in diseases characterized by neutrophilic, Th1- and Th-17-driven responses, such as COPD, multiple sclerosis, Crohn's disease and specific phenotypes of severe asthma; while CC chemokines shape leukocyte trafficking and function in Th2-dependent, eosinophil-rich inflammatory processes such as allergic asthma, early-stage atopic dermatitis, eosinophilic gastrointestinal diseases (Figure 2). Among

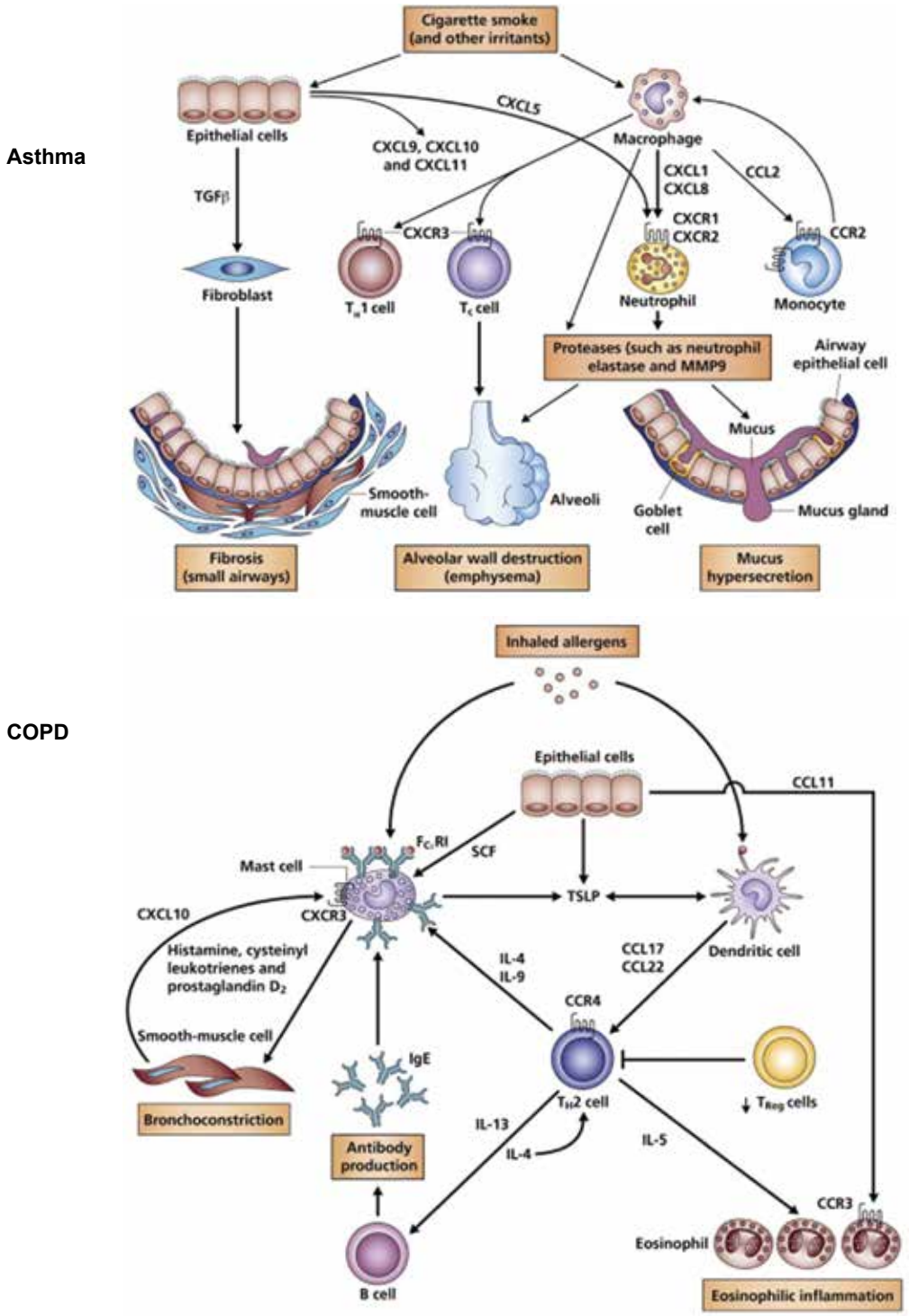

Figure 2 Involvement of chemokines and chemokine receptors in the inflammatory response present in bronchial asthma and COPD . In asthma, dendritic- and epithelial-derived chemokines elicited by the inhaled allergens recruit and activate Th2 cells and eosinophils through CCR4 and CCR3, respectively, contributing to the generation of an IgE-mediated inflammatory response. In COPD, chemokines released from lung epithelial cells and macrophages following exposure to cigarette smoke and/or pollutants generate a neutrophilic/monocytic-enriched infiltrate driven by Th1/Th17 cells that contributes to the inflammatory response and determins lung structural damage. (*Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Immunol, Barnes PJ, Immunology of asthma and chronic obstructive pulmonary disease, 8,183-192, copyright 2008.*)

the CC chemokines, CCL2/Monocyte Chemoattractant Protein-1 (MCP-1) is a non-redundant, potent regulator of monocytes, basophils and dendritic cells and participates to the Th2 polarization of memory T cells. The CX3C and the C subfamilies are represented by a single member, CX3CL1/fractalkine, which is the only cell membrane-associated chemokine, and lymphotactin, respectively.

Chemokines' range of regulatory competences has been widened over the last decades, as almost all cell types, including structural cells such as fibroblasts, endothelial and epithelial cells, as well as tumor cells have been found to express regulated profiles of functional chemokine receptors. By regulating cell proliferation, differentiation and apoptosis functions, and – either directly or indirectly – controlling angiogenesis and extracellular matrix remodeling, the chemokine system is also central to cancer-related inflammation, angiogenesis, tumor cell survival and invasiveness, and is critically involved in the step-wise process of wound healing.

Inhibition of leukocyte recruitment is a major mechanism of glucocorticoids' anti-inflammatory action and a major goal for novel therapies selectively targeting specific recruitment pathways. Antagonism of chemokine-mediated functions offers major challenges, partly due to member redundancy in each subclass, but mostly to the complexity of the control of their expression, which spans from transcriptional to post-translational and extracellular matrix-dependent mechanisms, that are diversely affected in specific disease settings. Antagonism of single chemokine receptors has so far shown only partial success as therapeutic strategy, and is now flanked by research toward more specific downstream regulatory pathways modulating the chemokine network.

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18 COMPLEMENT-MEDIATED REGULATION OF THE ALLERGIC RESPONSE

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KEY MESSAGES

- The phylogenetically ancient complement activation system is activated in the lungs of asthmatic individuals
- Several environmental triggers of asthma including allergens, air pollutants, cigarette smoke, and viruses activate the complement system and mediate Th2-driven immune responses
- Genetic polymorphisms in the C3 and C3aR1 genes are associated with susceptibility to the development of asthma in children and adults
- Modification of complement activation pathways may provide a novel strategy for the treatment of asthma

Asthma is thought to arise as a result of aberrant T helper type 2 (Th2)-polarized immune responses to innocuous environmental allergens, however the mechanisms driving these aberrant immune responses remain elusive. As a phylogenetically ancient immune system, the complement activation system, is a sophisticated network of soluble and membrane-bound proteins. It has evolved to recognize "danger or pattern-associated molecular patterns" expressed by foreign organisms through "hard-wired" pattern recognition receptors (PRRs). Activation of these PRRs culminates in the generation of C3 and the production of two pro-inflammatory anaphylatoxins, C3a and C5a, which induce inflammation and the membrane attack complex, which lyses foreign cells. The anaphylatoxins C3a and C5a are potent pro-inflammatory mediators that bind to specific cell surface receptors and regulate many processes observed in asthma including leukocyte activation, smooth muscle contraction, and mucus secretion.

Consistent with a role for C3-C3a in asthma, exposure to a variety of environmental triggers of asthma in animal models has been shown to directly activate complement at the airway surface. Genetic deletion of C3 in animal models has been shown to protect against the development of allergen-, pollutant-, and RSV-induced asthmatic responses and Th2 cytokine production suggesting that C3a production at the airway surface serves as a common pathway for the induction of Th2-mediated inflammatory responses thereby driving and/or exacerbating the disease (Figure 1, 2, 3). The exact mechanisms by which C3 regulates allergic responses are unknown, but current evidence suggests that C3a can both enhance antigen uptake by antigen-presenting cells, thereby enhancing sensitization to allergens, and initiate recruitment and activation of various inflammatory cells associated with asthma pathogenesis (Figure 4).

In humans, segmental allergen provocation resulted in a significant increase in C3a levels in the bronchoaveolar lavage of asthmatics, with no change in healthy volunteers. This differential production of C3a between individuals with asthma and those without asthma suggest that there may be alterations in the genetic control of the production of, the activation of, or the response to various complement components that may underlie susceptibility to asthma. Indeed, associations between single nucleotide polymorphisms (SNPs) in the C3 gene and atopic asthma

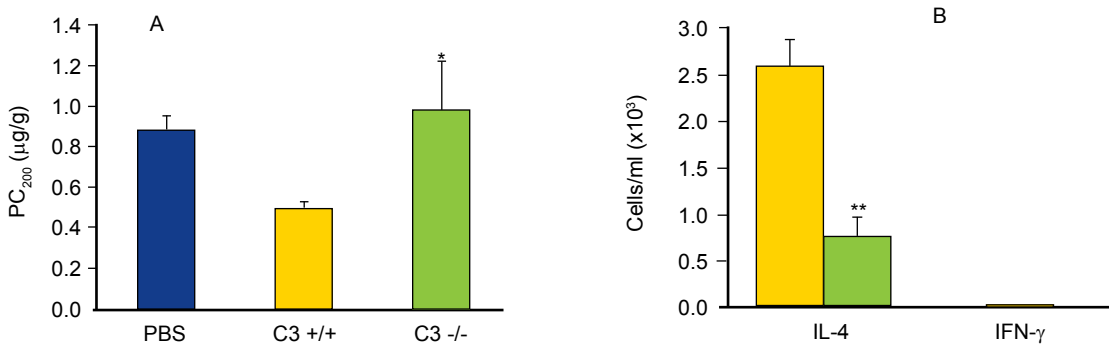

Figure 1 Allergen-induced asthma is C3 dependent. A) The effect of C3 deficiency on airway hyperresponsiveness (AHR) in anesthetized $C3^{-/-}$ and $C3^{+/+}$ mice. AHR was assessed 24 hrs after the last challenge and is expressed as the provocative concentration of ACh (in micrograms per gram) that increased baseline airway resistance 200% (PC_{200}). B) IL-4- and IFN-γ-producing cells in the lungs from $C3^{-/-}$ (■) and $C3^{+/+}$ littermates (□) were quantitated 24 h after the last Ag challenge. (*Reproduced from Drouin SM, Corry DB, Kildsgaard J, Wetsel RA. 167:4141-4145, Copyright 2001 with permission from the American Association of Immunologists.*).

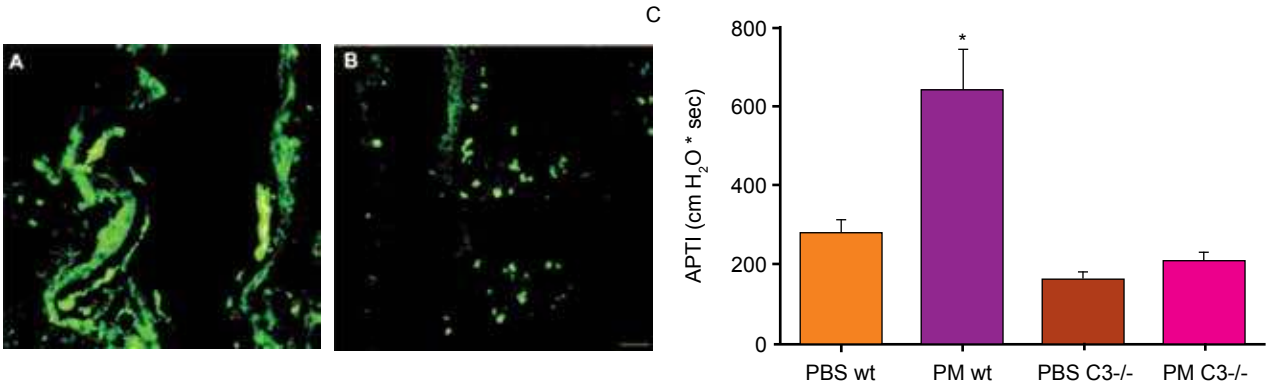

Figure 2 Air pollution exposure-induced airway hyperresponsiveness is C3-dependent. Lung sections from PM-exposed mice were stained with anti-C3 mAb (A) or (B) isotype control antibodies. Specific C3 staining is observed in the airway epithelial layer. C) Airway responsiveness (APTI) to acetylcholine stimulation is significantly reduced in C3-deficient mice after particulate matter (PM) exposure as compared to PM-exposed wildtype mice. ($P < 0.05$). (*Reproduced from American Journal of Respiratory Cell and Molecular Biology, the official journal of the American Thoracic Society, Walters DM, Breysse PN, Schofield B, et al., 27, 413-418, Copyright 2002 with permission from American Thoracic Society*).

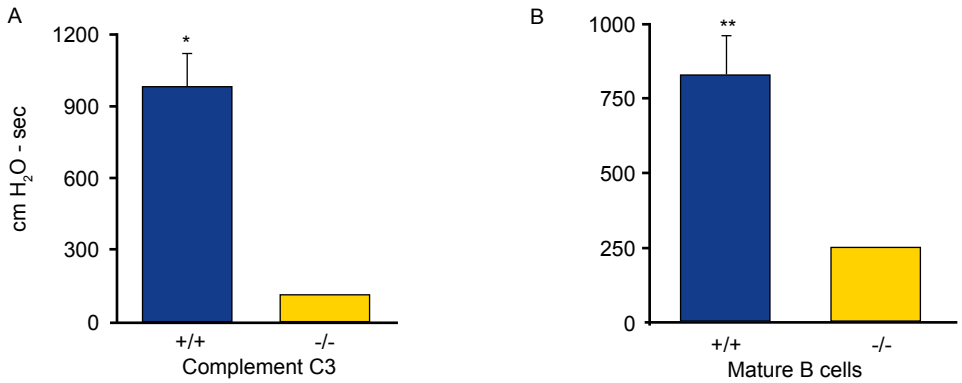

Figure 3 Respiratory syncytial virus-induced airway hyperresponsiveness is C3-dependent. Airway hyperresponsiveness in wildtype and C3- and B cell-deficient mice challenged with RSV 7 days after immunization with formalin-fixed RSV. (A) B6129F2 WT (C3+/+) and C3 deficient (C3−/−), and (B) C57BL/10 (B+/+) and B10 µMT (B−/−) mice. AHR to acetylcholine challenge is defined by the time-integrated rise in peak airway pressure. (*Reproduced from Journal of Experimental Medicine, Polack FP, Teng MN, Collins PL, et al., 196, 859-65, Copyright 2002 with permission from The Rockefeller University Press*).

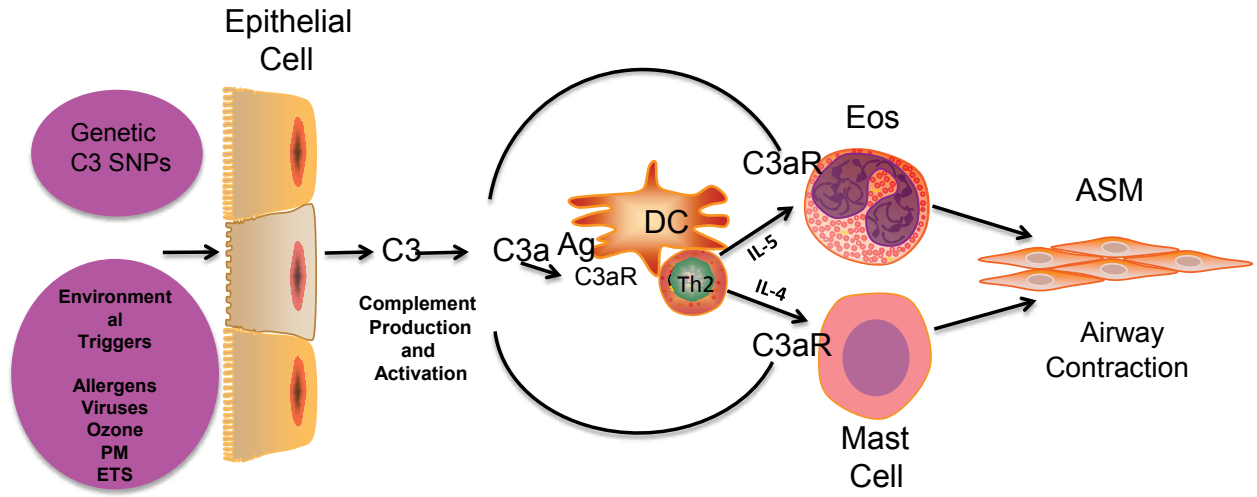

Figure 4 Complement activation pathways regulate Th2-mediated immune responses. Following airway exposure to a variety of environmental triggers of asthma in genetically susceptible individuals, C3 is produced and secreted by airway epithelial cells lining the airways. C3 is cleaved into its active form, C3a, presumably by proteases either contained in the allergens or produced by the epithelium. C3a then binds to its receptor, C3aR1 on antigen presenting cells, enhancing uptake of antigen by these cells. Antigen-loaded APCs then drive the differentiation of naïve T cells to Th2 cells. Th2 cytokines in turn recruit and active the effector cells of the allergic response, eosinophils and mast cells. During the effector phase of the response, C3a can bind its receptor on these effector cells enhancing their recruitment and activation. Growth factors and bronchoactive substances from these cells lead to increased airway smooth muscle growth and contractile capacity.

have been reported in children and adults. Interestingly, the frequency of these SNPs is high, suggesting that these polymorphisms may have conferred evolutionary advantage in the past and perhaps in protection from parasitic infections.

Although we are in the initial stages of understanding the role of complement pathways in asthma pathogenesis, one may postulate that changes in the activation of specific complement components due to differences in exposure to different environmental triggers or to genetic alterations in complement family genes or the convergence of both of these factors may play an important role in susceptibility to the development of allergic diseases. Further investigations into the mechanisms by which C3a modules allergic asthma may offer novel therapeutic approaches for the treatment of asthma.

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19 LIPID MEDIATORS OF HYPERSENSITIVITY AND INFLAMMATION

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KEY MESSAGES

- Lipid mediators regulate both the physiological status and inflammation in the airways
- Cysteinyl leukotrienes and prostaglandin D_2 are the best studied inflammatory mediators of hypersensitivity and allergic disorders
- Other lipid mediators, like pro-inflammatory eoxins and anti-inflammatory lipoxins also participate in allergic reaction
- A class of phospholipid and ceramide mediators interact with immune response in allergy

Since the discovery that bronchoconstriction and edema can be mediated by cysteinyl leukotrienes, lipid mediators attracted much attention in allergology. The biological effect of a lipid mediator is determined by its receptor affinity and intracellular signal transduction, and receptors differ in their specificity and cellular distribution. Lipid mediators of inflammation are difficult to study due to their complex metabolism, chemical similarities and rapid inactivation. Their levels in airways can be measured in bronchial or nasal lavage, induced sputum or exhaled breath condensate, while systemic production can be assessed in urine.

Regulation of the airways tonus, secretion or inflammation involves numerous mediators (Figures 1 and 2). Respiratory epithelium produces prostaglandin E_2 (PGE_2), secreted to the apical surface. It has been recently demonstrated that excessive PGE_2 can impair phagocytic clearance of solid particles by alveolar macrophages. A decreased number of carbon particles in alveolar macrophages and increased systemic production of PGE_2 metabolites were reported in children with asthma. Respiratory epithelium also secretes 15-hydroxyeicosapentaenoic acid (15-HETE) to its basal surface. Upon stimulation with Th2 cytokines (IL-4, IL-13), the asthmatic respiratory epithelium undergoes mucous cell metaplasia with amplication of the production of 15-HETE. 15-HETE can be metabolized to eoxins, isomers of cysteinyl leukotrienes. The concentration of eoxins (EXC_4, EXD_4 and EXE_4) is increased together with cysteinyl leukotrienes in children with asthma. Moreover, EXD_4 and EXE_4 leves correlate with bronchial hyperreactivity .

One of the asthma phenotypes is characterized by an overproduction of cysteinyl leukotrienes. These asthmatics have hypersensitivity to non-steroidal anti-inflammatory drugs and chronic rhinosinusitis. Patients with aspirin-exacerbated respiratory disease (AERD) overproduce prostaglandin D_2, but this finding is also present in other eosinophilic phenotypes of asthma. During an aspirin provocation test, bronchoconstriction is mediated by a further increase in the local and systemic production of cysteinyl leukotrienes, a unique feature of this disease.

The integrity of the lung function is maintained by PGE_2, which inhibits inflammation at physiological concentrations. PGE_2 can promote tissue injury in high doses.

Other lipid mediators are released by activated cells only. They act as highly bioactive autacoids capable of chemoattraction of neutrophils (12-HETE, leukotriene B_4)

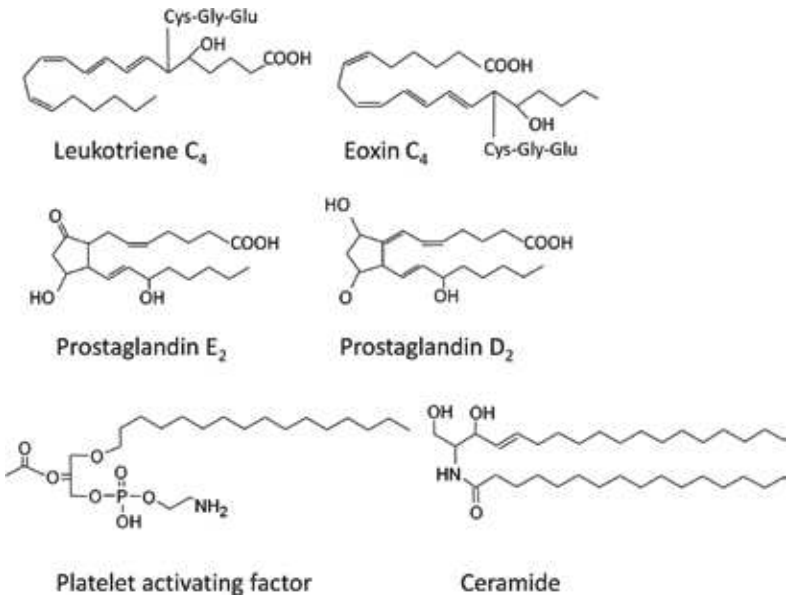

Figure 1 Main classes of inflammatory lipid mediators in the airways are cysteinyl leukotrienes, eoxins and prostaglandins. Platelet activating factor and ceramides are also released during allergic reaction.

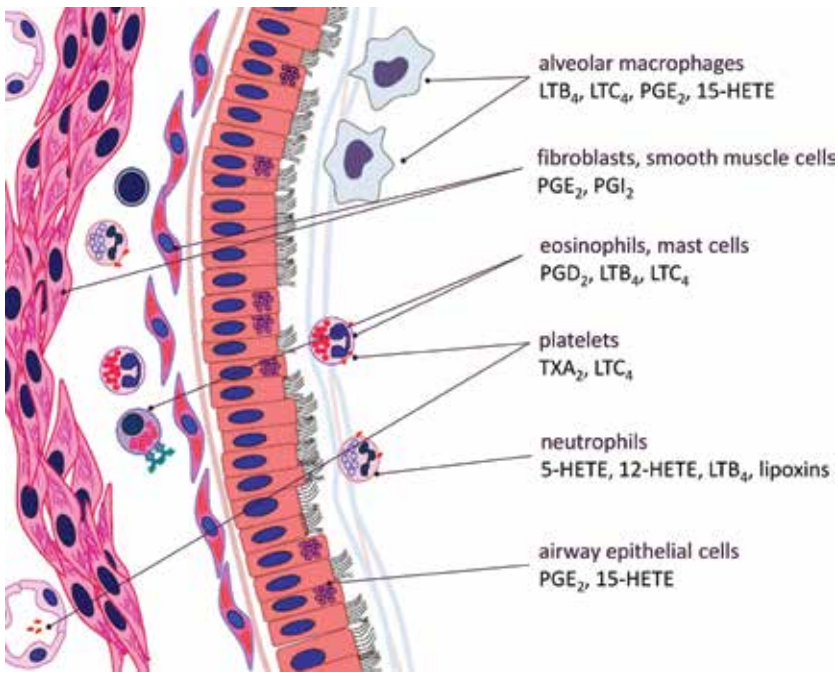

Figure 2 Lipid mediators are produced in airways by structural and inflammatory cells. In general, tissue infiltrating inflammatory cells produce pro-inflammatory mediators, while structural ones produce anti-inflammatory mediators. Excessive production of lipid mediators by respiratory epithelial cells and alveolar macrophages also promotes inflammation.

or eosinophils and lymphoid cells (PGD_2). Some can provide termination signals for inflammation (lipoxins, resolvins, protectins) and their biosynthesis requires cell interaction . Bioactive oxylipins are also generated from polyunsaturated fatty acids by reactive oxygen species in a non-enzymatic reaction. A separate class of lipid mediators are phospholipids and ceramides. Platelet-activating factor, a phosphatydylcholine ether of alkyl-acetyl glicerol is the most potent mediator of anaphylaxis and bronchoconstriction. Ceramides are abundant constituents of the cell membrane mediating apoptosis. Lipid mediators can bridge inflammation with the cellular immune response in allergic disorders.

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20 LIPID MEDIATORS IN RESOLUTION OF ALLERGIC INFLAMMATION

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KEY MESSAGES

- Non-resolving inflammation underlies the pathogenesis of allergic diseases
- Resolution of inflammation is an active, finely orchestrated and complex process
- Resolution of inflammation involves anti-inflammatory, immune regulatory, cell death and lipid mediator-related mechanisms
- ω3-derived specialized proresolving lipid mediators (SPMs) such as protectins, resolvins and maresins are key mediators of inflammation resolution
- Allergic diseases are associated with defects in the generation of SPMs
- Synthetic SPMs or compounds triggering their production are promising therapeutics for the treatment of allergic diseases

Persistent non-resolving inflammation underlies the pathogenesis of allergic diseases including rhinitis and asthma, and determines both the intensity of the symptoms and the chronicity of the disease. Yet, the mechanisms controlling resolution of inflammation have only recently started to become elucidated.

Resolution is an active and highly orchestrated process of similar complexity to the onset and progression of inflammation. It starts early in the inflammatory response and involves the induction of anti-inflammatory/regulatory networks aiming at terminating pro-inflammatory signalling, and biosynthetic circuits triggering the production of specialized proresolving lipid mediators (SPMs) essential for return to homeostasis. The relative balance between pro-inflammatory, anti-inflammatory and proresolving responses, influenced by environmental exposures and lifestyle factors, eventually determines whether the inflammatory response will persist or terminate.

Central to the resolution of inflammation are bioactive lipids derived from ω3 and ω6 polyunsaturated fatty acids (PUFA). The early oxygenation of arachidonic acid into prostaglandins and leukotrienes that occurs during the initiation of an inflammatory response is followed by the generation of lipoxins, lipids with anti-inflammatory and proresolving properties, in a process termed 'lipid mediator class switching'. As the inflammatory response progresses, the production of additional SPMs derived from ω3 PUFAs such as protectins, resolvins and maresins ensues (Figure 1). These act in a stereospecific manner through G protein-coupled receptors to reverse vasodilation and suppress leukocytic cell infiltration, de-activate inflammatory cells, promote apoptotic cell and tissue debris clearance, and repair damaged tissue, altogether leading to the restoration of homeostasis.

Notably, ω3-derived SPMs also possess antimicrobial function. PD1 is induced by antiviral TLRs and exhibits potent antiviral activity, while several resolvins and protectins enhance antibacterial defences. This has significant implications for the role of lipid mediators in allergic disease exacerbations, which are often triggered by infections. The biosynthesis of SPMs is dependent on lipoxygenase-5 and lipoxygenase-12,15,

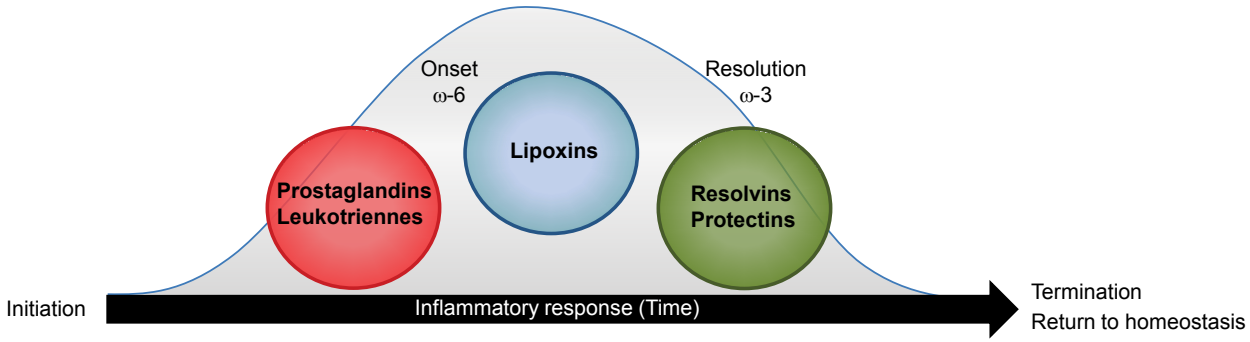

Figure 1 Generation of eicosanoids and specialized proresolving lipid mediators as inflammation progresses. As the inflammatory response proceeds, the production of additional proresolving lipids derived from ω3 PUFAs such as protectins, resolvins and maresins ensues. These act in an orchestrated manner to terminate inflammation and ensure the transition to homeostasis.

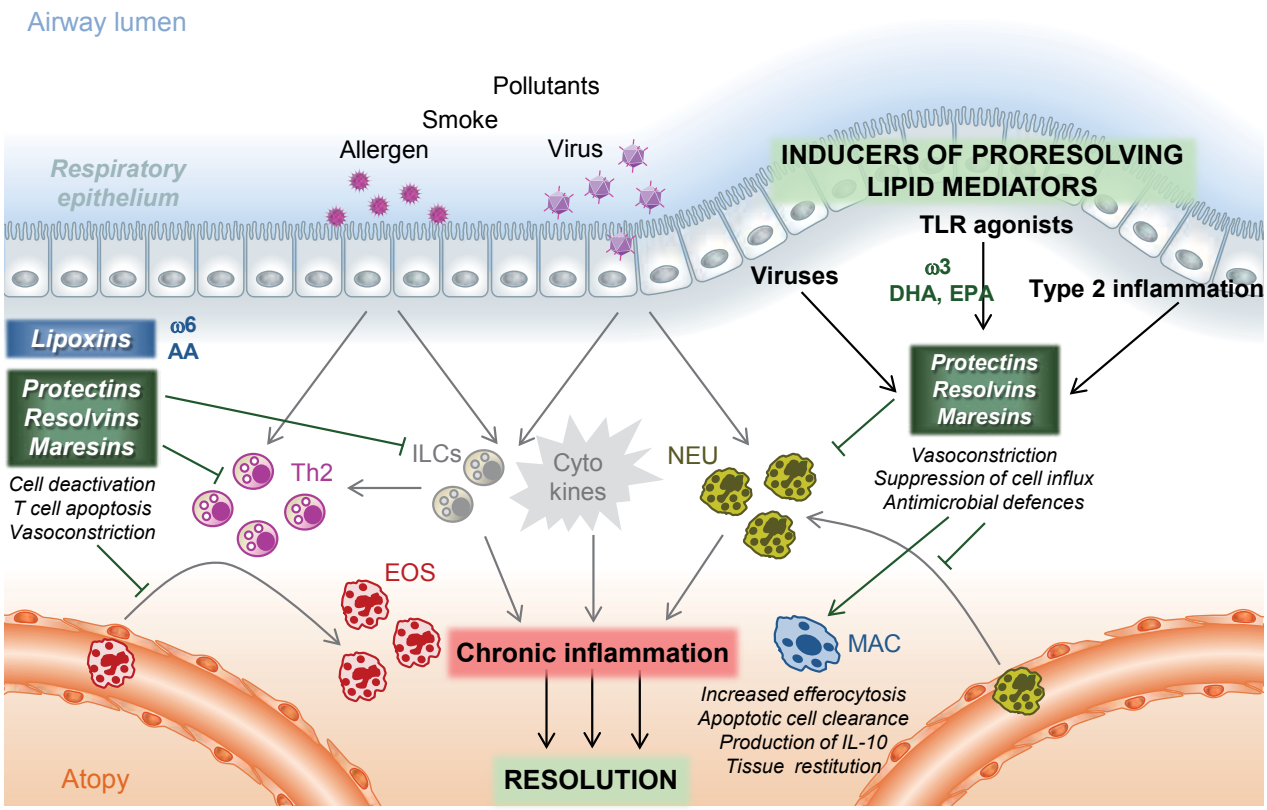

Figure 2 Proresolving activities of ω3/ω6 polyunsaturated fatty acid (PUFA)-derived bioactive lipids in respiratory allergies. Specialized proresolving lipid mediators (SPMs) are generated in response to viral infection, Toll-like receptor (TLR) stimulation or type 2 inflammation. SPMs act in concert to reverse vasodilation, prevent leukocytic cell infiltration, de-activate inflammatory cells including Th2 cells and innate lymphoid cells (ILCs), upregulate macrophage efferocytic function and antimicrobial defences, promote clearance of apoptotic cells and debris, and repair damaged tissue, eventually restoring homeostasis. AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EOS, eosinophil; MAC, macrophage; NEU, neutrophil. (Adapted *from Andreakos E. Asthma exacerbations: a molecular dichotomy between antiviral and pro-inflammatory responses revealed.;EMBO Mol Med. 2012;4(12):1231-3. Reprinted with permission under the Creative Common Attribution License or equivalent.*)

key enzymes that carry out the oxygenation of PUFAs. Substrate availability, temporal expression and activation of these and other key enzymes ultimately determine which SPMs will be produced, where and when.

There is emerging evidence that SPMs are essential for the resolution of allergic inflammation. Lipoxin A4 (LXA4) has been found in nasal secretions of patients with allergic rhinitis or chronic rhinosinusitis, as well as bronchoalveolar lavage and exhaled breath condensate of patients with asthma, and low LXA4 levels have been linked to the severity of the disease. LXA4 has also has been shown to inhibit IL-13 production by human innate lymphoid cells and resolve allergic inflammation in rodents. Similarly, protectin D1 (PD1) has been detected in exhaled breath condensate from patients with asthma, and low PD1 levels have been observed during acute exacerbations. PD1 and resolvins D1 and E1 have been further used to promote resolution of allergic airway inflammation in experimental mouse models. On the basis of current data, SPMs can affect multiple processes during an allergic response as depicted in Figure 2. In conclusion, although it its early days, the field of resolution of inflammmation raises expectations for the application of SPMs or substances triggering their production for the treatment of allergic diseases.

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21 ALLERGY AND THE EPITHELIAL BARRIERS

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Asthma is a disorder largely restricted to the conducting airways characterised by episodic bronchoconstriction superimposed on a background of airway hyperesponsiveness and is generally responsive to bronchodilator drugs. Airway inflammation is another characteristic of asthma which, to a variable extent, is responsive to corticosteroids and often associated with allergy.

This concept of allergy driving an IgE, mast cell and eosinophilic inflammation in asthma has been heavily underpinned by involvement of the Th2 subtype of T cells capable of releasing an array of cytokines and chemokines linked to the allergic cascade.

However, this simplistic approach has not been rewarded by therapeutics targeting individual components of the allergic cascade, which while identifying selective subgroups of "responders", has not provided a ubiquitous series of treatments where "one size fits all". These less than encouraging findings raise the question whether the current Th2 model for asthma adequately explains the disease in its very wide range of manifestations.

KEY MESSAGES

- The epithelium in chronic asthma resembles a chronic wound with impaired barrier function
- This manifests as enhanced susceptibility to injury by viruses, pollutants and allergens and aberrant repair to sustain inflammation and remodelling
- Recapitulation of morphogenetic epithelial growth and transcription factors suggest persistent activation of the epithelial mesenchymal trophic unit (EMTU)
- A new approach to prevention and treatment might aim to increase airway resilience rather than focusing on suppressing inflammation once present
- Inadequate epithelial tight junction assembly has been demonstrated in asthma, atopic dermatitis and chronic rhinosinusitis

ACTIVATION OF THE EPITHELIAL MESENCHYMAL TROPHIC UNIT

In addition to inflammation, the pathology of asthma is dominated by structural changes including epithelial damage and mucous metaplasia, angiogenesis, smooth muscle proliferation and angiogenesis. In 2000, we proposed that these structural features were the consequence of the airways resembling a chronic wound in which epithelial damage is accompanied by aberrant production of growth factors and mediators that not only drive remodelling, but also sustain chronic inflammation (Figure 1). We referred to this interaction as activation of the epithelial mesenchymal trophic unit (EMTU) since many of the signalling mechanisms are similar to those engaged in lung morphogenesis in the developing foetal lung.

ENHANCED SUSCEPTIBILITY OF THE ASTHMATIC EPITHELIUM TO INJURY

The airways in chronic asthma are more susceptible to injury as revealed by the majority of novel genes discovered by GWAS being preferentially expressed in the epithelium. There is also strong genetic and gene expression evi-

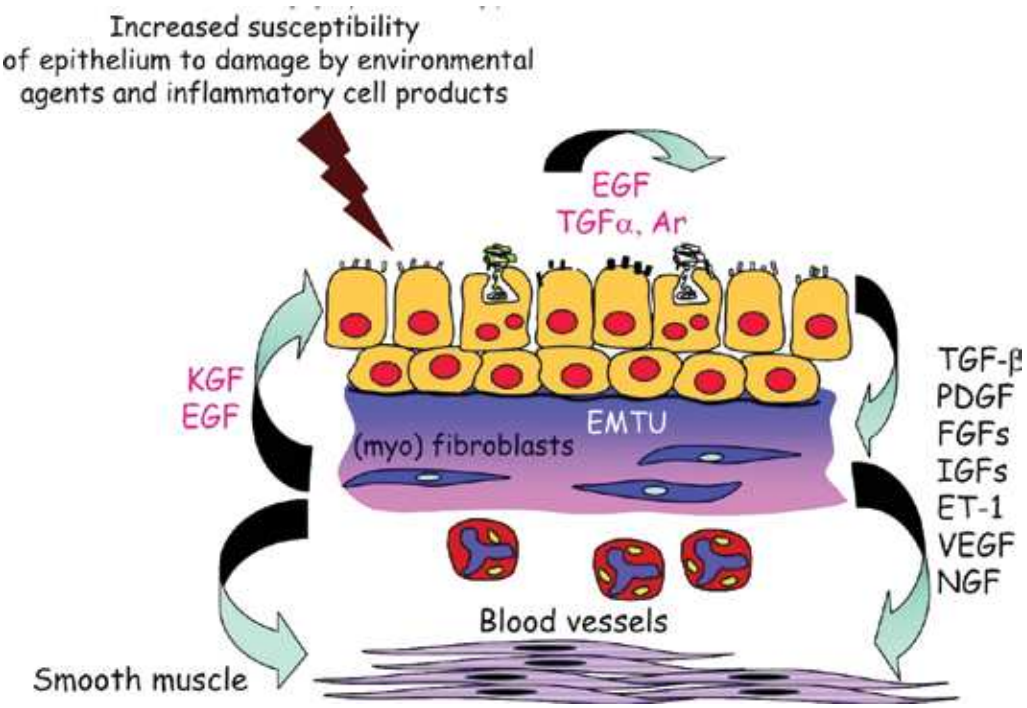

Figure 1 Schematic representation of the activated epithelial mesenchymal trophic unit (EMTU) in active asthma. Increased susceptibility of the epithelium to environmental injury such as biologically active allergens, respiratory viruses and pollutants together with a delayed repair response leads to the secretion of a range of growth factors, cytokines and chemokines that both drive airway wall remodelling and sustain chronic airway inflammation. (*From Holgate S.T. Arshad SH, Roberts GC, Howarth PH et al. A new look at the pathogenesis of asthma. Clin Sci. 2009; Reprinted with permission under the Creative Common Attribution License or equivalent.*)

dence that anti-oxidant pathways in the asthmatic airways are defective leading to enhanced tissue damage on exposure to viruses and pollutants. Even under basal conditions, the asthmatic epithelium shows enhanced expression of biomarkers of apoptosis (e.g. caspases, P85 fragment of PARP) indicating loss of resilience.

Asthmatic airways, both in children and adults, are more vulnerable to common and usually innocuous respiratory viruses such as rhinoviruses (RVs) adenoviruses and coronaviruses. When infected with major or minor subclass RVs, asthmatic epithelial cells fail to eliminate the virus adequately leading to enhanced replication, shedding and cytotoxic cell death with pro-inflammatory mediator release. Such a mechanism explains viral exacerbations of asthma, the relatively weak effect of corticosteroids and the mixed neutrophilic/eosinophilic inflammatory profile. The primary defect appears to be in the first step of induction of the anti-viral protective cytokines interferons (IFNs) β and λ after ds viral RNA binds to microsomal TLR3 (Figure 2). At least part of this defect can be accounted for by the enhanced basal production of TGFβ to reduce SMAD3 phosphorylation and increase nuclear inhibitory signals provided by SOCS1 and 3. Since exogenous IFNβ could restore defective anti-viral defence to asthmatic epithelium in vitro, inhaled IFNβ could be a novel therapeutic for severe exacerbations. Indeed, when administered at the first sign of a common cold in severe asthma inhaled IFNβ1α given daily for 14 days almost abolishes the post-viral exacerbation in parallel with maintaining biomarkers of anti-viral defence in respiratory secretions.

THE ASTHMATIC EPITHELIUM DISPLAYS IMPAIRED HEALING

The epithelium also contributes to persistence of asthma through enhancing remodelling pathways in the form of aberrant epithelial repair. Over expression of the epidermal growth factor (EGF) family of receptors and their phosphorylation in the asthmatic epithelium increases in proportion to disease severity and is not accompanied by appropriate proliferative responses as a consequence of mobilisation of cell cycle inhibitors such as P_{21}^{waf} to the epithelial nuclei where they inhibit cell cycling. The net result of this is delayed epithelial

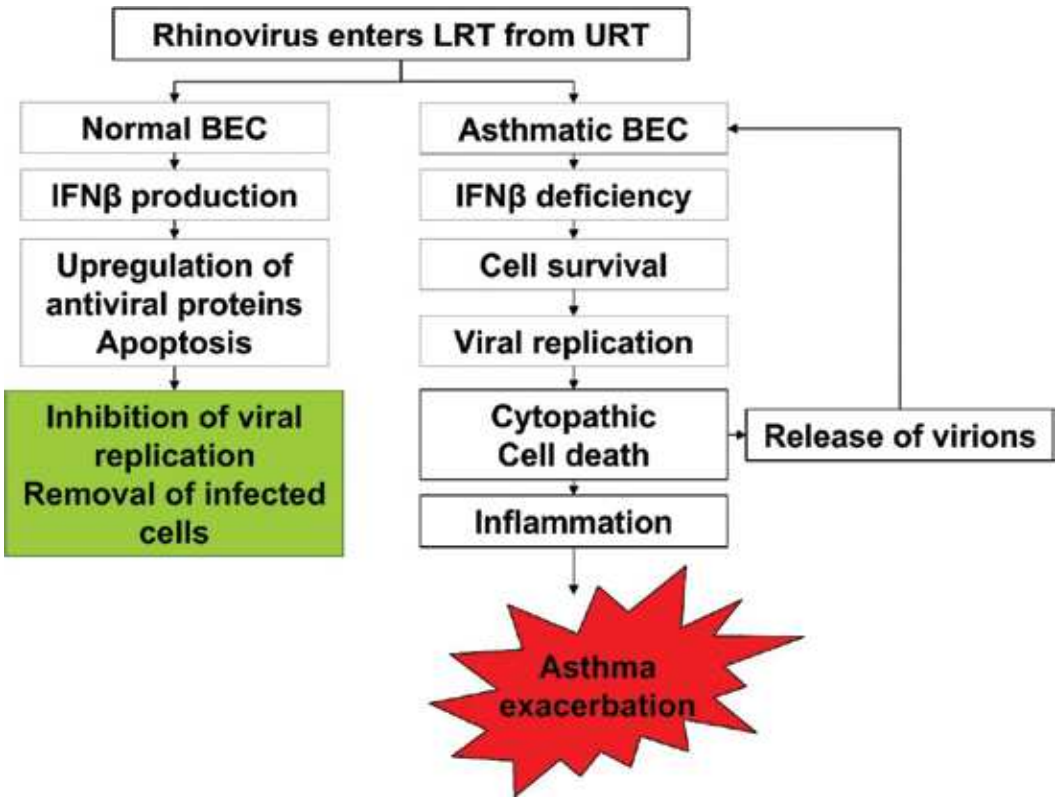

Figure 2 In chronic asthma, there is a defect innate immunity at the level of defective production of interferons when toll-like receptors such as TLR3, TLR5 and TLR7 become activated by viral nucleic acids as the first step in triggering an anti-viral response. This results in virus survival, replication and eventual cytotoxic destruction of epithelial cells with release of inflammatory mediators that contribute to exacerbations. The defect appears to be in Step 1 of the anti-viral cascade involving defective interferon regulatory factor (IRF) 3 signalling to the interferon genes with low production of IFN induction, reduced signalling via the common IFN receptor and, therefore, reduced IRF7 amplification of the antiviral cascade in Step 2. The IRF7 pathway itself remains intact. For this reason a small amount of exogenous IFNβ acting via the common IFN receptor can restore a full anti-viral response as shown in the left bottom panel. It is upon this principle that inhaled IFNb1ais being developed for the prevention/treatment of severe asthma exacerbations. (*From Holgate S.T. Arshad SH, Roberts GC, Howarth PH et al. A new look at the pathogenesis of asthma. Clin Sci. 2009; Reprinted with permission under the Creative Common Attribution License or equivalent*).

healing following environmental insults and enhanced pro-fibrotic, myogenic and angiogenic growth factor production such as TGFβ PDGFs, IGFs, FGFs and VEGFs to drive structural remodelling (5). The epithelium of asthmatic children displays similar characteristics and when grown as a monolayer and physically injured displays slower and incomplete restitution suggesting that the abnormality is intrinsic to the asthmatic epithelium irrespective of age.

INADEQUATE EPITHELIAL TIGHT JUNCTION ASSEMBLY IN ASTHMA

There is increasing evidence that the epithelial barrier function is persistently deranged in asthma at the level of junctional integrity. The defective barrier function in asthmatic epithelium persists in differentiated epithelial cell cultures following repeated passage indicating an intrinsic abnormality linked to enhanced mucous metaplasia, reduced cilia-genesis and reduced innate immune responsiveness. Increased permeability is enhanced by T cell interactions within the epithelium as well as the actions of "biologically active" allergens (e.g. proteases), viral infection and pollutant exposure, all of which perturb tight junction functions.

IS ASTHMA A DISORDER OF EPITHELIAL SENSING OF THE INHALED ENVIRONMENT?

Such a "pro-asthmatic" epithelium may have its origin in the way the epithelium senses the inhaled environment, with altered sensitivity being predetermined through altered expression of transcription factors involved in foetal lung morphogenesis such as SPDEF increase secondary to FoxA2 and NKX2-1 (TTF-1) decrease. Pathway analyses have now shown that in addition to regulating the "set point" for epithelial mucus production, the same transcription factors are also implicated in orchestrating innate immune de-

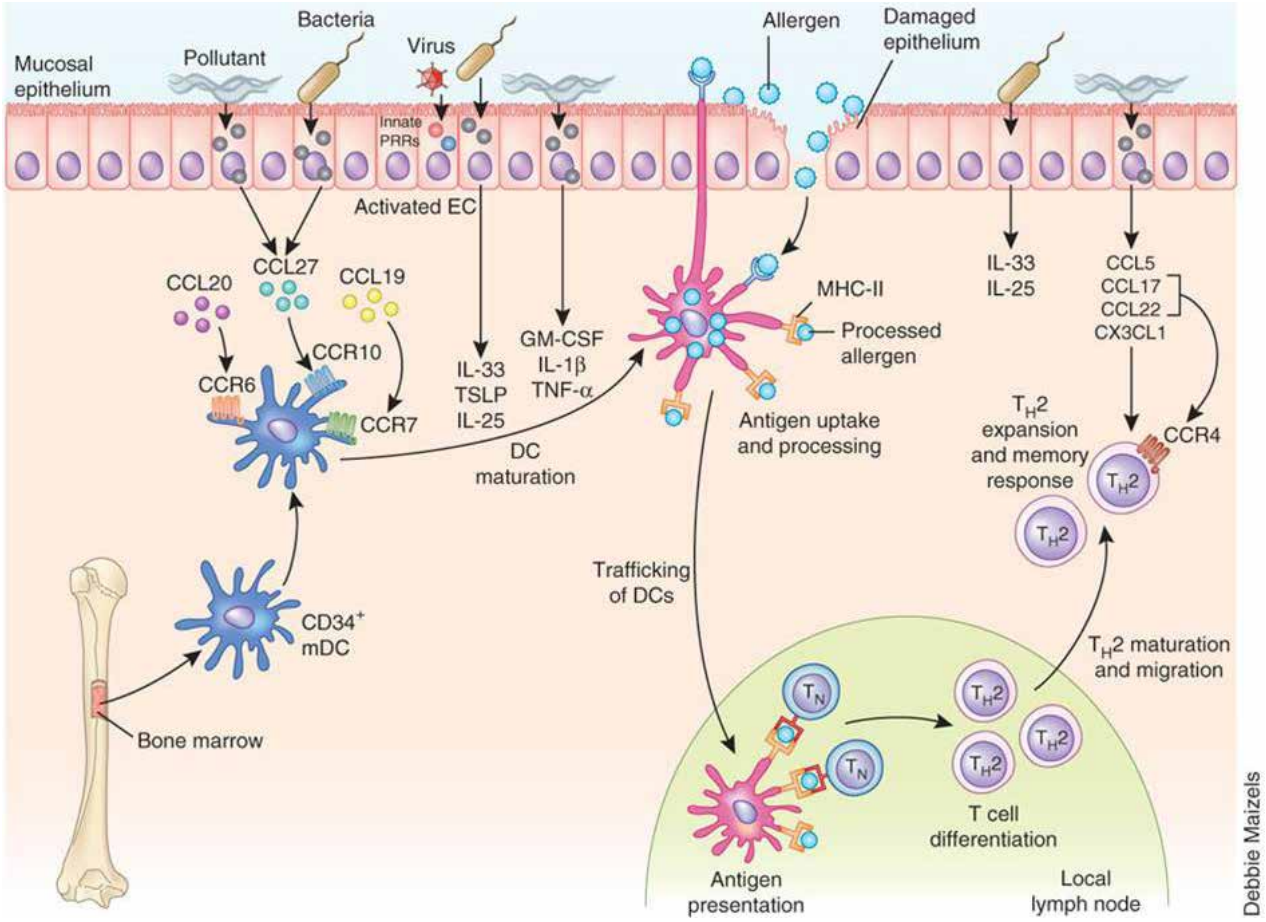

Figure 3 Schematic representation of the role of epithelial transcription factors involved in morphogenesis of the foetal lung such as SPDEF, FoxA2 and TTF1 interacting with key transcription factors of the allergic cascade such as STAT6 in driving mucous metaplasia and orchestrating both chronic Th2-type inflammation and tissue remodelling. In asthma, the 'set' point for responding to environmental insults is altered to reduce airway resilience and augment the chronic wound scenario depicted in figure 1 and on the right side of the above figure. (*Reproduced with permission from Holgate S.T. The sentinel role of the airway epithelium in asthma pathogenesis. Immunol Rev 2011; 242: 205-219, with permission from Willey Blackwell.*).

fence (including IFN responses to viral infection) and inflammatory pathways such as those leading to Th2-type allergic responses (Figure 3).

This leads to the overall conclusion that the different asthma subtypes have their origin in the way the airway epithelium "reads" the environment and translates this along discrete pathways to variable disease manifestations and responses to interventions.

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22 EPITHELIAL PROTEASES AND ALLERGIC DISEASES

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KEY MESSAGES

- Proteases are physiologically important digestive enzymes and generate peptides from precursor proteins. However, both proteases and protease inhibitors can be active players in inflammation
- Proteases can be endogenous and exogenous. Almost all inhalant allergens such as pollens, mites and fungi have protease activity.
- Proteases exert their activity through Protease Activated Receptors, PAR 1-4, which are highly relevant in asthma and other allergic diseases
- Proteases disrupt tight junctions between the cells, can penetrate into the tissue and directly activate the cells apart from the classical flow of immunological mechanisms

Proteases are composed of a group of molecules with diverse physiological and pathological effects. The human body is equipped with a variety of protease inhibitors that counteract and thus control the activity of proteases. However, these protease inhibitors can be active participants of inflammation.

Proteases are naturally present in all organisms. Depending on their catalytically active site, they are termed as serine, cysteine, aspartic and metalloproteases. Endogenous proteases are produced by inflammatory cells, most importantly by mast cells (chymase, tryptase), neutrophils (cathepsin, elastase) and epithelial cells (thrombin). Almost all allergens including house dust mites, pollens, fungi and cockroach and many bacteria, such as staphylococcus aureus, and viruses such as rhinovirus and influenza have significant protease activities.

Physiologically, proteases function as digestive enzymes, generate active peptides from their precursors and drive innate immunity against multicellular organisms such as parasites, which are too large to be phagocytosed. They also participate in pathological processes including allergic diseases (Table 1).

The action of proteases can be mediated through Protease Activated Receptors (PAR) 1-4. They are G protein-coupled receptors and are present almost on all cell types. PAR-dependent action of proteases results in: increased release of pro-inflammatory cytokines by epithelial cells, endothelial cells, inflammatory cells, keratinocytes and fibroblasts; enhancement of IgE production; angiogenesis; increased cell migration, infiltration and degranulation of inflammatory cells; proliferation and contraction of airway smooth muscle cells; proliferation and activation of goblet cells and increased mucous production (Figure 1).

Some activities of proteases are PAR-independent and are basically a function of exogenous proteases. They increase pro-inflammatory cytokine production by airway epithelial cells, activate eosinophils and increase mucus production.

Their highly relevant activity for allergic diseases is the effect of proteases on epithelial tight junctions and adhesion molecules. Through their ability to disrupt occludin and claudin molecules and to activate MMP9 (which activates other cellular proteases),

TABLE 1

Proteases in inflammation

Source	Protease	Mode of action	Actions
Exogeneous	Pollens Fungi Mites Cockroach Hymenoptera Bacteria Viruses	PAR dependent PAR independent	Disruption of tight junctions Disruption of barrier function Th-2 adjuvants Secretion of pro-inflammatory cytokines Promotion of IgE synthesis Activation of epithelial cells keratinocytes inflammatory cells airway smooth muscle
Endogenous	Thrombin Plasmin Tyrptase Chymase Plasmin Kallikrein Trypsin Elastase Cathepsin G	Mostly PAR dependent	Activation of Endothelial cells Epithelial cells Keratinocytes Fibroblasts Airway smooth muscle All inflammatory cells Glandular secretion

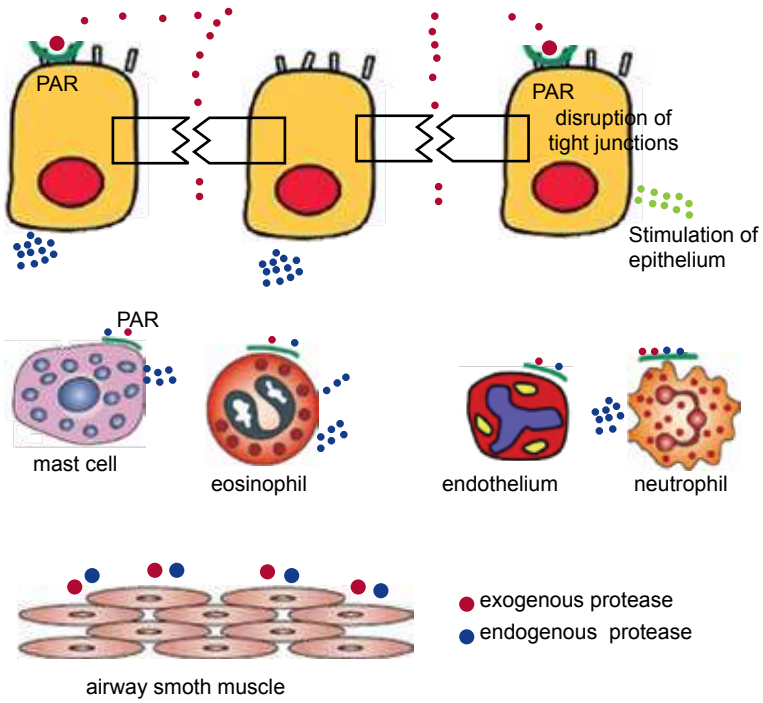

Figure 1 The action of proteases mediated trough Protease Activated Receptors (PAR).

proteases can penetrate through the intracellular junctions in the mucosal epithelial barrier and epidermis. This allows the penetration of the allergenic molecules into the tissues, where they can exert their protease as well as immune stimulating activities. This recently emerging concept raises the intriguing possibility that protease activities of the allergens may be critical not only for the maintenance of tissue inflammation observed in allergic diseases, but may also be important in the inception of allergic diseases. In addition, this initial penetration may be subsequently followed by the stimulation of a variety of cell types without the classical IgE and other cellular immune mechanism.

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23 MECHANISMS OF IMMUNE REGULATION IN ALLERGY

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KEY MESSAGES

- Immune tolerance to allergens have been studied in individuals receiving allergen-specific immunotherapy (AIT) and high dose allergen exposure models such as beekeepers and cat owners
- Early basophil and mast cell desensitisation is the first event of immune tolerance to allergens
- Induction of allergen-specific T regulatory (reg) cells characterized by the expression of multiple suppressor factors; CD25, CTLA-4, PD1, RUNX, HR2, IL-10 and TGF-beta is essential
- Induction of IL-10-producing Breg cells after high dose Ag exposure and AIT was described, together with increased allergen-specific IgG4 production, which is specifically confined to IL-10-producing Breg cells
- Decreased eosinophil, mast cell and basophil migration and activation in the affected tissues also occurs during allergen tolerance

Allergy is characterized by dominant allergen-specific Th2 responses, and consequent IgE induction. Many factors influence the pathophysiology of allergic diseases, including genetic susceptibility, route/time/dose of allergen exposure, structural features of the allergen and microbial exposure.

The immunoregulatory mechanisms that can mediate tolerance towards allergens in humans have been subject to intensive research during the last decades. These mechanisms have been studied in allergic patients receiving allergen-specific immunotherapy (AIT) as well as in healthy individuals, who are exposed to high-doses of allergens, such as beekeepers and cat owners. These human *in vivo* models have demonstrated that the mechanisms leading to peripheral tolerance to allergens include early desensitization of mast cells and basophils, induction of T regulatory (reg) and Breg cells, regulation of allergen-specific immunoglobulin production and interference with migration and activation of eosinophils, mast cell and basophils in the allergic tissues.

Treg and Breg cells play a key role in the induction and maintenance of tolerance towards allergens. These cells produce immunoregulatory cytokines such as IL-10 and TGF-β. TGF-β is a pleiotropic cytokine that has a wide range of functions including suppression of B and T cell proliferation and differentiation, as well as control of airway inflammation and airway remodeling. IL-10 is a key anti-inflammatory cytokine, which inhibits effector T cell activation directly through suppression of co-stimulatory pathways in T cells, and indirectly through suppression of antigen-presentation capacity of DCs. IL-10 also suppresses mast cell and eosinophil activation, thereby interfering with early and late phase allergic responses. Both Treg and Breg cells contribute to IgG4 production and suppression of IgE production. Inducible IL-10-producing B regulatory 1 (Br1) cells are skewed towards the production of anti-inflammatory IgG4 antibodies. These cells may play a role in tolerance induction to allergens, as an increase in the frequency of IL-10-producing B cells specific for

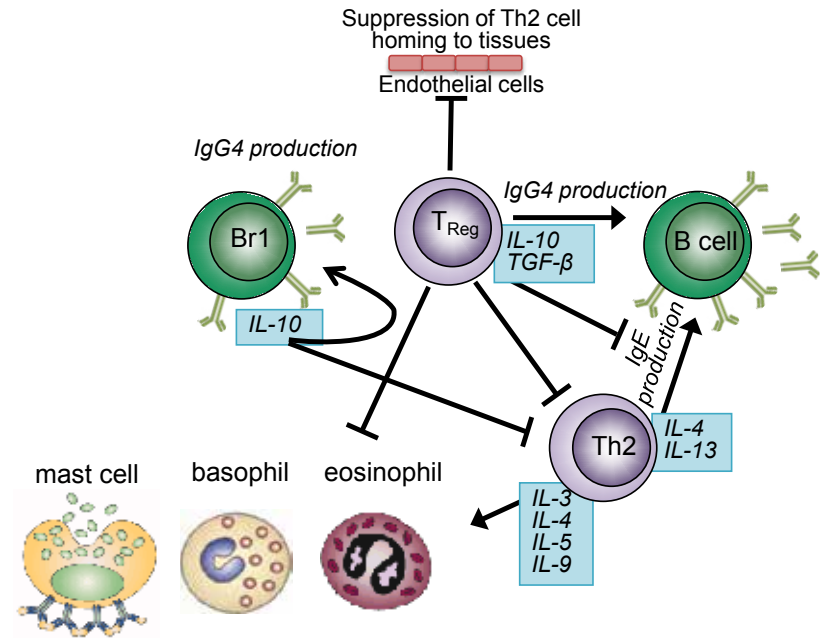

Figure 1 Role of Treg and Breg cells in the suppression of allergic inflammation. Treg cells and their cytokines mainly IL-10 and TGF-β suppress Th2 type immune responses and control allergic diseases in many ways. Black arrows show the regulatory and suppressive effects of Treg cells on: B cells by inducing IgG4 and IgA and suppressing IgE; on Th2 cell by suppressing proliferation and homing to tissues; on mast cells, basophils and eosinophils via direct and indirect suppressive effects; and on epithelial cell activation and proinflammatory properties by direct and indirect suppression. In addition, Br1 cells, which produce IL-10 suppress effector T cells and contribute to IgG4 synthesis.

the bee venom allergen phospholipase A2 was observed in bee venom allergic patients, who received AIT.

The susceptibility of mast cells and basophils to allergen-induced degranulation is reduced already after the first injection of AIT. This may be the result of subclinical levels of degranulation of these cells caused by allergen, leading to the increased activation thresholds observed during in vitro measurements. Furthermore, rapid up-regulation of histamine receptor (HR) 2 was observed in basophils during the first 6 hours of venom immunotherapy. HR2 triggering could suppress FcεRI-mediated basophil degranulation. Histamine can be released from mast cells and basophils that are activated during AIT and can regulate T cell responses as well. HR2 negatively regulates both Th1 and Th2-type responses. Therefore, HR2 appears to be a key mediator in the suppression of Th2 responses and induction of tolerance towards allergens. Intensive research in the area is essential to fully uncover the molecular pathways of allergen tolerance.

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24 NEURO-IMMUNE REGULATION OF ALLERGIC INFLAMMATION

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KEY MESSAGES

- Dysbalanced neurogenic responses may contribute to the pathogenesis of allergic diseases and other inflammatory diseases
- The axon reflex participates in the acute inflammatory response in rhinitis or asthma and is aggravated in asthmatic patients, due to a high degree of neuronal plasticity
- Increased neurotrophin levels were described in the asthmatic patients where they play a critical role in maintaining eosinophilia and Th2 driven inflammation, mast cell activation and enhance IgE production by B cells
- There is an urgent need for the development of biomarkers assessing the state of neurogenic dysregulation in asthmatic patients together with the development of novel therapeutic approaches aiming to re-establish the neurogenic homeostasis

The pathophysiology of asthma is complex and heterogeneous showing inter- as well as intra-individual variability. In addition to the profound dysregulation in innate and adaptive immune functions, dysbalanced neurogenic responses substantially contribute to the disease (Figure 1).

Airway hyper-responsiveness is considered a hallmark of asthma. The contractility of airway smooth muscle cells is controlled by several types of neurons including sympathetic (adrenergic), parasympathetic (cholinergic) and non-adrenergic, non-cholinergic (NANC) neurons. These types of neurons are part of the complex innervation network of the airways and the lung.

Neurons control lung function via the axon reflex (Figure 2). This is best described for sensory neurons, which pick up stimulatory signals in the airways and transmit them via the sensory neurons to the central nervous system (CNS). Stimuli able to excite these neurons include unspecific pollutants such as tobacco smoke particles, ozone and NO2 as well as signals driven from microbes and allergens. Cell damage caused by viral infection and replication is an im-

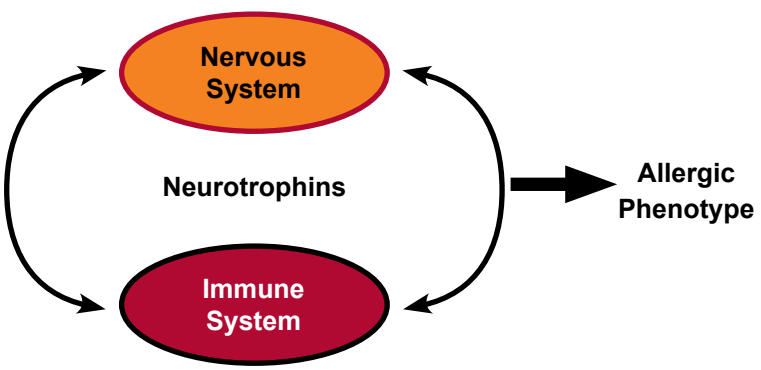

Figure 1 Neurotrophins contribute to bi-directional communication between nervous and immune system.

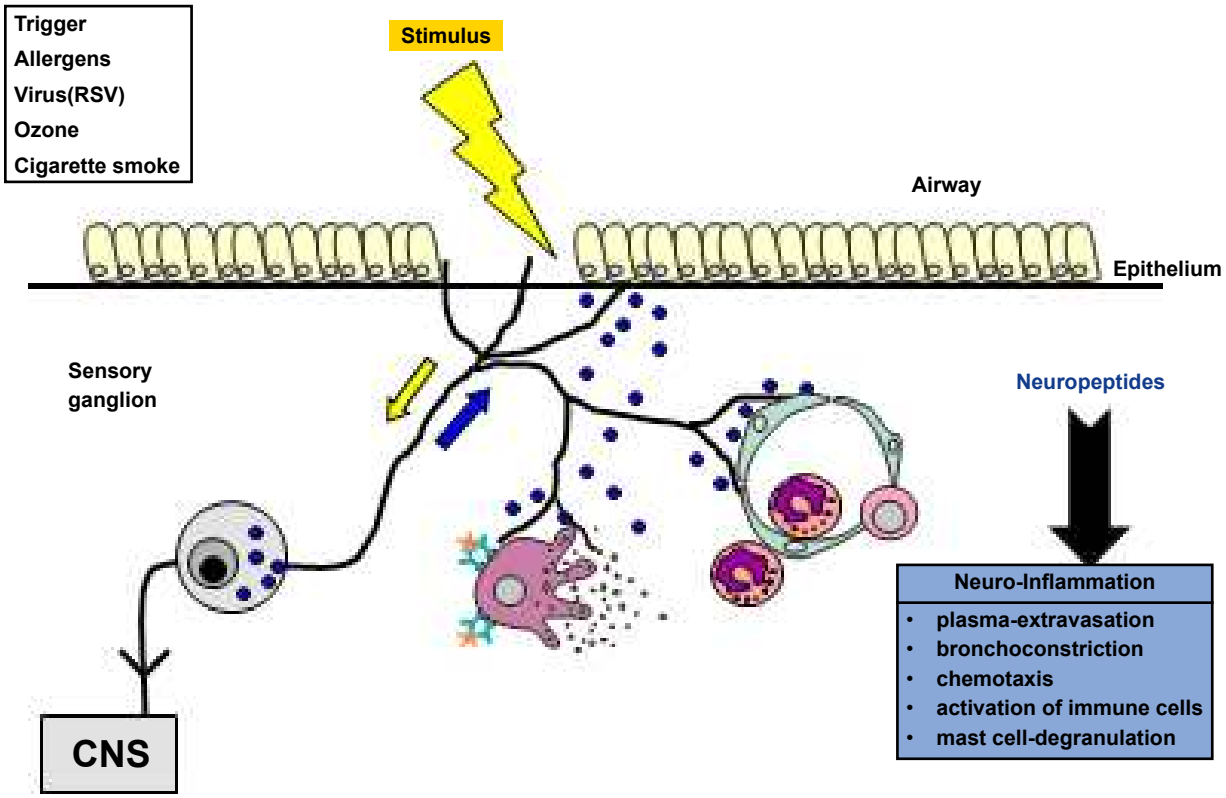

Figure 2 Neurogenic inflammation – The axon reflex.

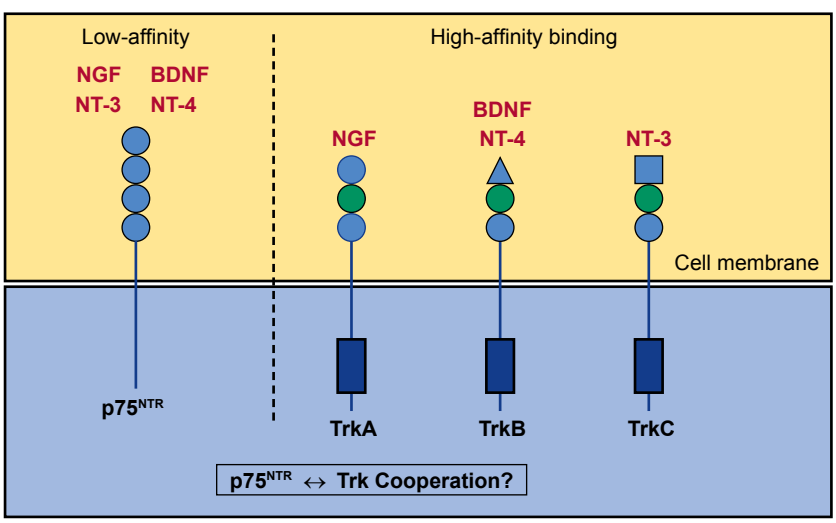

Figure 3 Neurotrophins and receptors.

portant trigger of the axon reflex. Efferent signals are sent back from the cell body of the neurons to the lung periphery. Within the cell bodies, neuropeptides are produced and stored. Afferent firing of the neurons triggers not only the production, but also the retrograde transport of these neuropeptides back to the site of irritation and activation. These locally released peptides (including tachykinins, neurokinins and others) play an important role in mediating acute pro-inflammatory events such as vasodilatation, recruitment of inflammatory cells, activation of mast cells and eosinophils and others. Therefore, the axon reflex is one important example of how neurons actively participate in the acute inflammatory response in rhinitis or asthma.

TABLE 1

The family of NGF and its receptors in bronchial asthma
❖ augmentation of TH-2 inflammation (NGF, p75)
❖ anti-apoptic signals (NGF, BDNF, p75) • eosinophils • pulmonary plasma cells
❖ acute broncho-constiction (NGF, p75)
❖ neuronal control of airway hyperresponsiveness (BDNF)
❖ epithelial wound healing

The axon reflex is aggravated in asthmatic patients, due to a high degree of neuronal plasticity observed in many chronic diseases. The development of the peripheral neuronal network, the state of activation, and the differentiation of neurons and various subtypes is tightly controlled by another group of mediators termed neurotrophins (Figure 3). Neurotrophins belong to a family of mediators, which control neuronal functions and exert also important effector mechanisms on many other cells including immune cells. The prototype of the neurotrophin family is the nerve growth factor (NGF). The brain-derived neurotrophic factor (BDNF) and other members of this family have also been extensively studied. Neurotrophins signal through two different types of receptors, the pan-neurotrophin-receptor p75 and the high-affinity neurotrophin receptors TRKA, B and C. These receptors are also expressed at various degrees and extend on cells of the innate and the adaptive immune system.

An important step forward in better understanding the neurogenic component in asthma was the description of increased neurotrophin levels in asthmatic patients (observed in sputum, BAL, tissue, blood). Further mechanistic studies carried out both in human and mice models further revealed that NGF and BDNF play a critical role in maintaining eosinophilia and Th2-driven inflammation, mast cell activation, while enhancing IgE production by B cells. Therefore, neurotrophins are considered major players in the overall maintenance of an already existing inflammatory response (Table 1).

There is an urgent need for the development of better diagnostic tools to assess the state of neurogenic dysregulation in asthmatic patients. The development of novel biomarkers should go hand in hand with the development of novel therapeutic approaches aiming to re-establish neurogenic homeostasis in this disease.

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25 UNITED AIRWAYS AND IMMUNE REGULATION

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KEY MESSAGES

- The upper and lower airways are often diseased together
- A high percentage of young children with asthma are sensitized to inhalant allergens
- There is an increased risk of developing late-onset asthma in chronic rhinosinusitis patients
- These patients are often non-atopic, but express IgE to staphylococcal enterotoxins
- Apart from inhalant allergens, staphylococcal enterotoxin–specific IgE is related to asthma

It is well established that the upper and lower airways are linked together, we therefore, call them "United Airways". The development of asthma mostly begins early in life time, and asthma manifests before the age of 16 years; usually, this early-onset asthma is preceded by rhinitis symptoms. Over 80% of young children with asthma are allergen sensitized, and atopy in this age group increases disease morbidity. Additionally, atopy plays a critical role in the inception of asthma attacks in this age group, in particular during viral infection. Also in later life, rhinitis is a powerful predictor of asthma, and atopy significantly increases the risk for asthma development in late-onset asthma.

A recent Europe-wide epidemiologic study on the prevalence of chronic rhinosinusitis (CRS), a disease manifesting in the nose and paranasal sinuses, confirmed the well-known association between allergic rhinitis and early-onset asthma, but also demonstrated a clearly increased risk of suffering from late-onset asthma in CRS patients. Thus, whereas younger patients with asthma frequently complain of allergic rhinitis symptoms, older patients with asthma often suffer from sinus disease with symptoms such as nasal obstruction, loss of smell and facial pain/headache. CRS can be differentiated into CRS without nasal polyps (CRSsNP) and with nasal polyps (CRSwNP), based on symptoms (loss of smell is typical for CRSwNP, headache and facial pain are typical for CRSsNP), nasal endoscopy (presence of bilateral nasal polyps) and CT scanning. From those phenotypes, CRSwNP has a clearly increased risk of asthma comorbidity in Caucasian populations.

Allergic airway disease is characterized by the mucosal synthesis of IgE molecules, which arm dendritic cells and mast cells. These armed cells upon contact with the allergen, release specific mediators and cytokines. With the Th2 cells being prominent, an eosinophilic type of inflammation is orchestrated, which involves key interleukins (ILs) such as IL-4 and IL-5. Very similar mechanisms, although patients with CRSwNP often are non-atopic, also prevail in late-onset asthmatics with sinus disease. Among the group of nasal polyps, especially the IL-5 positive endotype, predominantly showing an eosinophilic inflammation, bears a high risk of asthma comorbidity (up to 70%). In these patients, serum total IgE often is increased, independent of the atopic status of the patient. IgE antibodies to Staphylococcus aureus superantigens (SE-IgE) can be detected in a large proportion of these patients in the upper air-

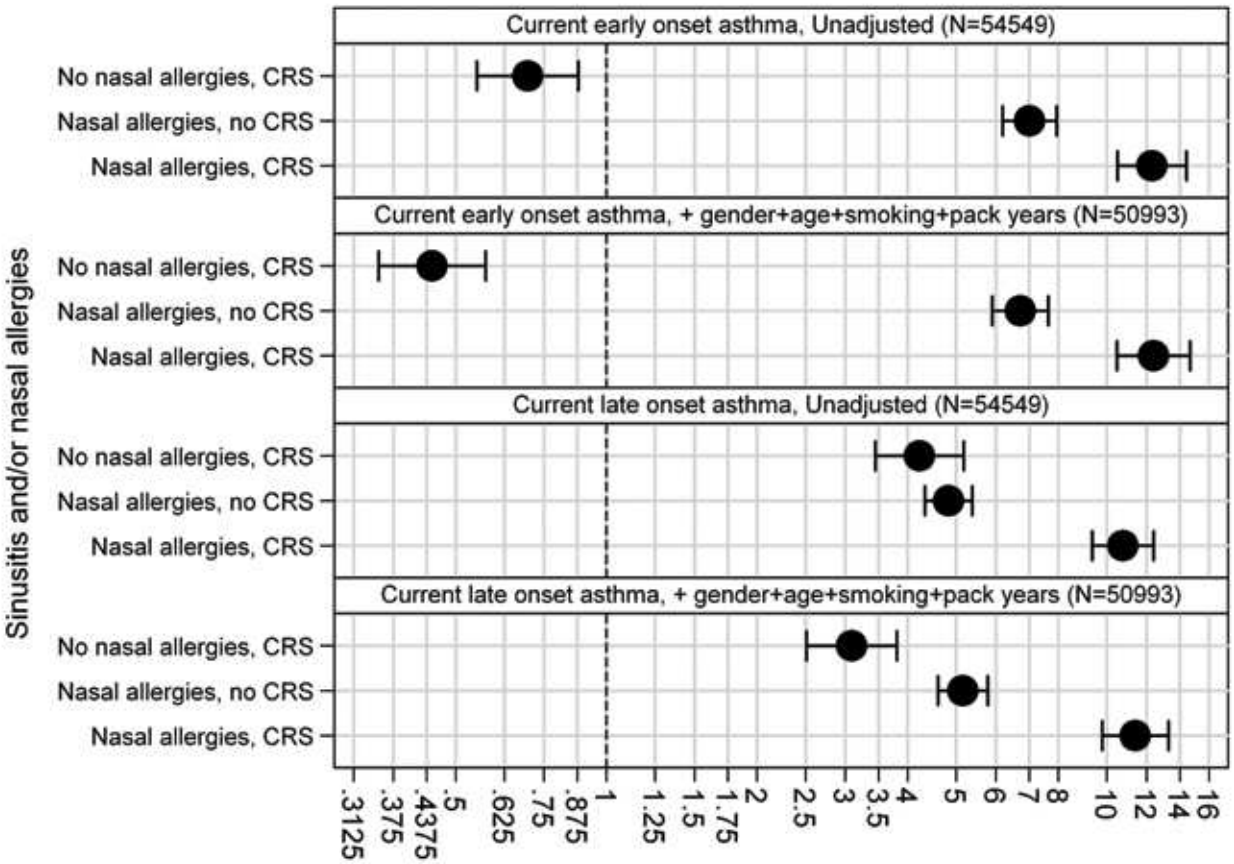

Figure 1 The association (relative risk ratio with 95% confidence interval) of early- and late-onset asthma with nasal allergies (early-onset) and chronic rhinosinusitis (late-onset). (*Reproduced with permission from Jarvis D, Newson R, Lotvall J,et al. Asthma in adults and its association with chronic rhinosinusitis: The GA2LEN survey in Europe. Allergy 2012;67:91-98, with permission from Willey Blackwell*)

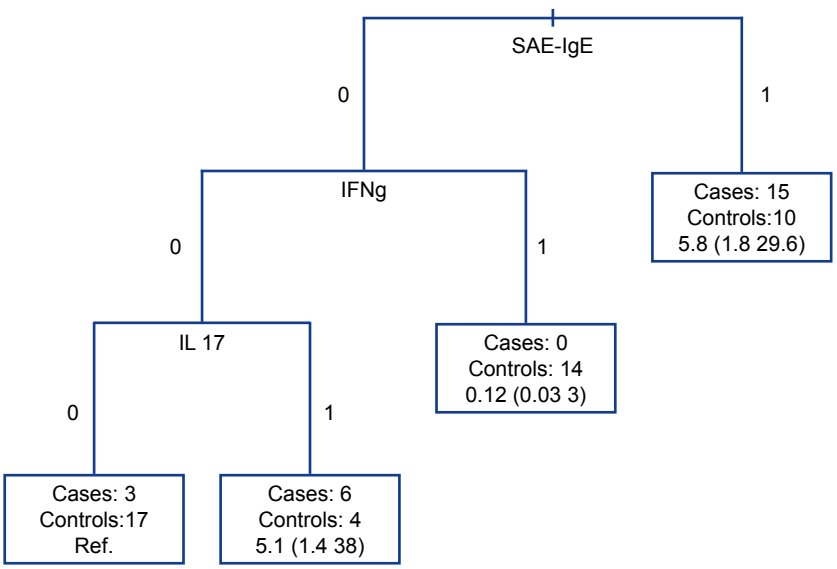

Figure 2 Classification tree for comorbid asthma in patients with nasal polyps: SE-IgE positivity (categorical classifying determinant) is associated with a significantly increased risk to suffer from co-morbid asthma. (*Reprinted from J Allergy Clin Immunol, 126/5, Bachert C, Zhang N, Holtappels G,Presence of IL-5 protein and IgE-antibodies to staphylococcal enterotoxins in nasal polyps is associated with co-morbid asthma, 962-968, Copyright 2010, with permission from Elsevier.*)

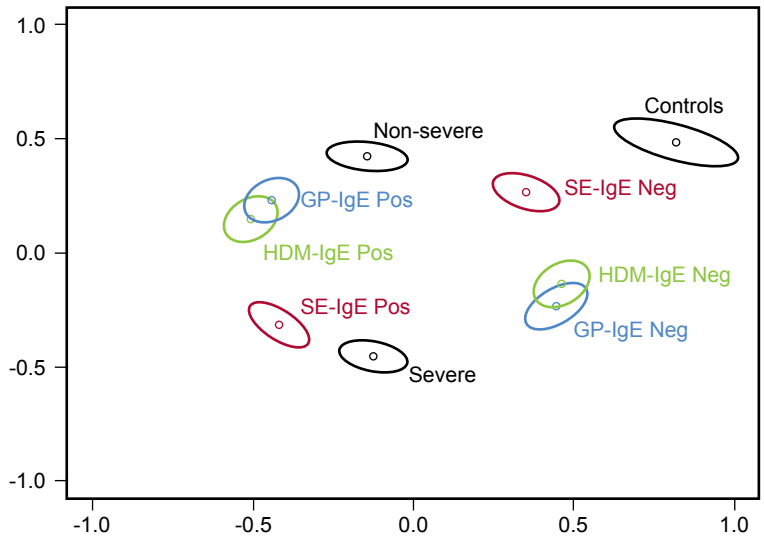

Figure 3 Multiple correspondence analyses factor map with 95% confidence ellipses situating relationships between parameters and disease severity. SE IgE is situated near severe asthma, whereas GP and HDM IgEs are situated near non-severe asthma. (*Reprinted from J Allergy Clin Immunol, 130/2, Bachert C,van Steen K, Zhang N,Specific IgE against Staphylococcus aureus enterotoxins: an independent risk factor for asthma, 376-381, Copyright 2012, with permission from Elsevier.*)

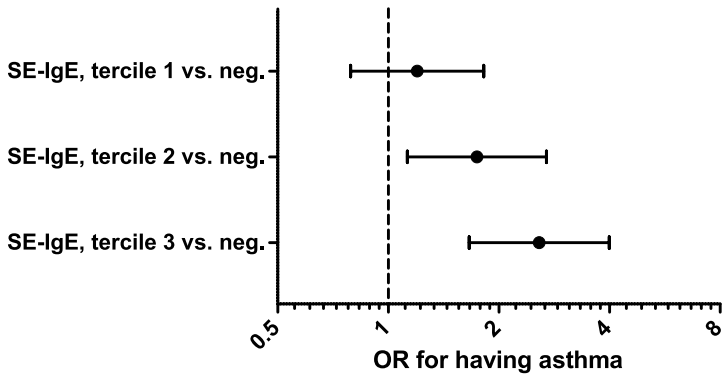

Figure 4 Odds ratios for asthma presence for each of the tertiles of serum SE-IgE in a pan-European study involving app. 3000 patients. The concentration of SE-IgE is significantly associated with an increased risk of suffering from asthma (*Reproduced with permission from Tomassen P, Jarvis D, Newson R, et al. Staphylococcus aureus enterotoxin specific IgE and its association with asthma in the general population: a GA²LEN. Study. Allergy 2013;68:1289-97, with permission from Willey Blackwell.)*

ways, but also with increasing severity of asthma in serum. SE-IgE antibodies are significantly associated with severe asthma, oral corticosteroid use and hospitalizations within the last 12 months, and lung function parameters.

As well as IgE antibodies to inhalant allergens, SE-IgE antibodies are also associated with an increased risk of asthma in the general European population, according to a recent epidemiologic study investigating more than 55000 patients. Local IgE therefore needs to be recognized as an important mediator of disease of the airways.

Diagnostic tools in asthma should include questions on nasal and sinus symptoms, blood eosinophils, total IgE and specific IgE abs to inhalant allergens and SEs also in non-atopic subjects. The treatment of the upper airways in these patients might furthermore support the management of the lower airways, and therefore should be part of the individual therapeutic strategy.

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26 GENETICS OF ALLERGY

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KEY MESSAGES

- Epidemiological and genetic research has provided firm evidence for the existence of genetic determinants of atopic diseases with reported heritability estimates of up to 80%
- Atopic diseases are complex, polygenic traits, influenced by multiple disease genes
- Results from studies using high density association mapping suggest that epithelial events and innate immune function are major drivers of pathogenesis
- The detection of molecular interactions between susceptibility genes and environmental triggers over time and the elucidation of epigenetic factors as potentially underestimated source of hidden heritability will be major tasks for the next years

Atopic diseases (eczema, asthma, rhinitis) affect an increasing number of individuals worldwide and represent a major global health problem. Epidemiological and genetic research has provided firm evidence for the existence of genetic determinants of atopic diseases with reported heritability estimates of up to 80% (Figure 1). Atopic diseases are typical complex, polygenic traits, which are thought to be influenced by multiple disease genes. As for other complex traits, the identification of these genes is hampered by considerable phenotype and locus heterogeneity, incomplete penetrance and interaction with mostly unknown non-genetic factors, as well as by the yet incompletely understood interrelation of these diseases with each other and with intermediate traits like IgE. Only recently, it has become possible to systematically unravel the polygenic etiology of complex human diseases by high density association mapping, which has allowed a breakthrough in the definition of disease genes with an unprecedented richness of findings and a surprisingly high degree of reproducibility. For allergic diseases, results from such studies suggest that epithelial events, e.g. hereditary alterations of structural proteins and innate immune function are major drivers of pathogenesis. With the exception of few single loci exerting large effects on some phenotypes, e.g. filaggrin null mutations on atopic dermatitis (Figure 2), the majority of loci displays rather modest effects when considered in isolation, and the despite impressive progress in the field, only a small proportion of the total heritability is yet explained by known risk variants. It is further becoming clear that genetic risk factors overlap between traditional entities rather than providing direct discriminators suggesting shared and potentially intermediate molecular mechanisms of immune mechanisms and inflammation and illustrating the need for a more accurate classification of allergic diseases based on their phenotypic and molecular basis (Figure 3). Of note, the observed increase in prevalence of atopic diseases is not primarily genetic, but rather due to the dramatic changes of environmental conditions and modern health hazards that trigger a genetic vulnerability into action. The detection of molecular interactions between susceptibility genes and environmental triggers over time and the elucidation of epigenetic factors as potentially underesti-

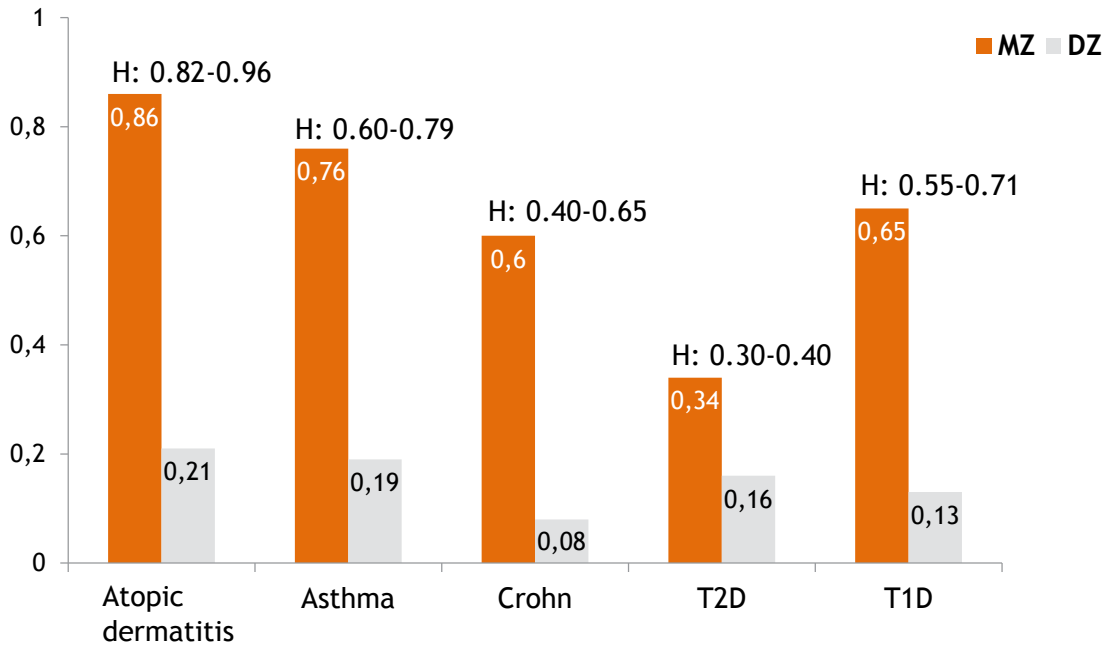

Figure 1 A genetic predisposition to the development of asthma, allergic rhinitis, and atopic dermatitis (AD) has been confirmed by numerous epidemiological studies with the strongest evidence delivered by twin studies, which show a distinctly higher concordance rate among monozygotic twins as compared to dizygotic twin pairs (for AD: 0.72-0.77 vs 0.15-0.23), and segregation analyses, which suggest that genetic factors account for more than 80% of the variance in the susceptibility to AD.

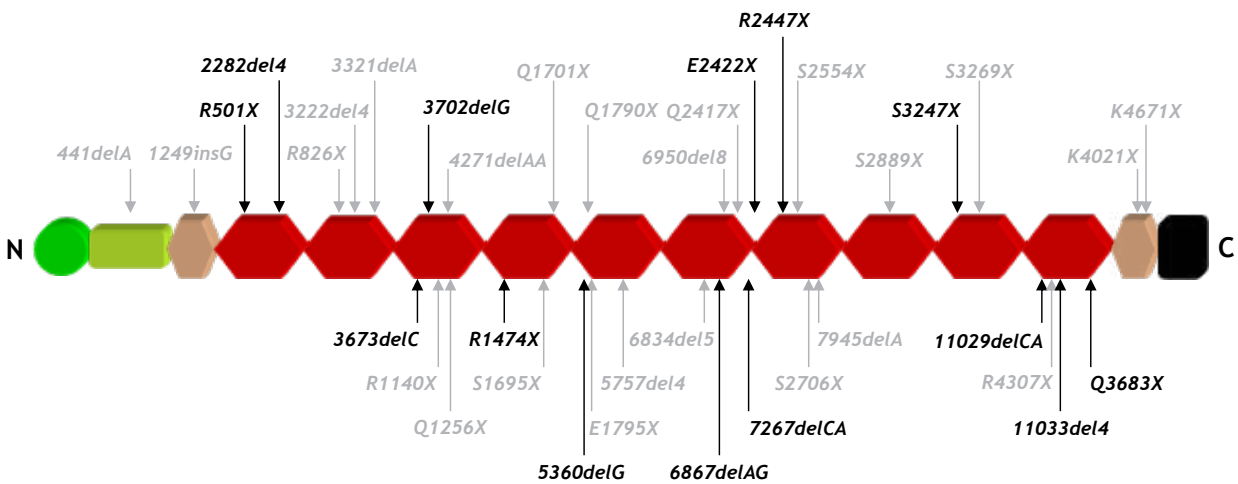

Figure 2 The strong association of low-frequency FLG null mutations with atopic dermatitis is one of the most robust genotype-phenotype linkages observed in complex human genetic disorders, and illustrates the importance of epithelial barrier defects in the development of allergic disease.

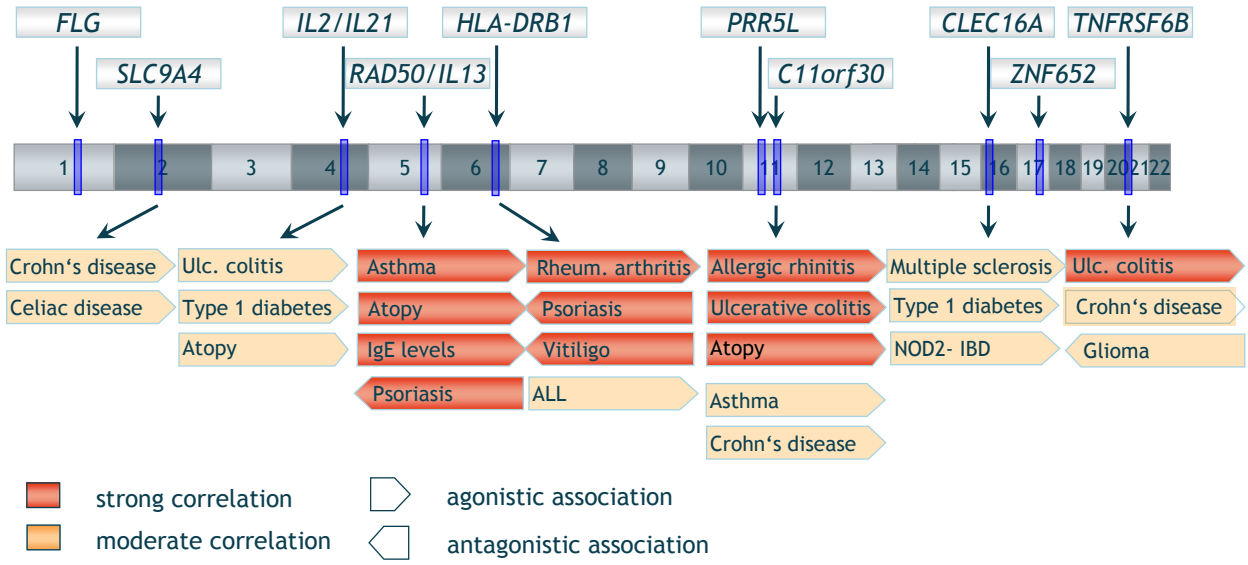

Figure 3 The majority of established risk loci for atopic dermatitis are also implicated in the development of other immune mediated-diseases with both agonistic and antagonistic effects.

mated source of this hidden heritability will be major tasks for the next years.

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27 EPIGENETICS OF ALLERGY

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KEY MESSAGES

- Epigenetic modifications result in changes in the expression of genetic material and can occur by three processes: DNA methylation, histone modification or microRNA mediated changes
- Like genetics, epigenetic marks are inherited with each cell division and can persist through generations and may account in part for the increased prevalence of allergic disease
- Genes in immune cells responsible for disease can be epigenetically modified by variables such as environmental exposures, diet, and the microbiome
- Identical twins with discordant asthmatic status have been shown to have different epigenetic marks on key immunologic genes in their genome

Epigenetics is the study of heritable changes in gene activity that are not caused by changes in the DNA sequence (Figure 1). These include modifications to the structure supporting the DNA called histones. Histone modification (adding or removing acetyl groups) determines DNA packaging and the cell's ability to access and read the associated sequence. DNA can also be modified directly by adding a methyl group to cytosine bases, which may restrict access to the DNA for transcription into mRNA. Finally, gene expression can be regulated at the post-transcriptional level by microRNAs, which can further modify mRNA transcripts and histones to alter the expression of genes (Figure 2).

Many environmental factors are thought to regulate gene expression through these mechanisms and studies are ongoing to identify specific exposures and pathways of effect (Figure 3). One of the main characteristics of epigenetic changes is that it is passed on to daughter cells with each cell division so it may have a long lasting effect on cell function.

The importance of epigenetics in determining allergic phenotype was illustrated in identical twin studies, in which one twin suffered from asthma and the other did not. Asthmatic twins were found to exhibit DNA methylation patterns that differed from their healthy counterpart. Most notably, they had increased methylation and decreased expression of the FOXP3 gene, which is important for the anti-inflammatory function of T regulatory cells. Additionally, they showed decreased function of non-allergic effector T cells through methylation of the IFN-gamma gene.

Furthermore, there is evidence that some epigenetic marks can be transmitted from parents to children trans-generationally, with cumulative effect over multiple generations (Figure 4). This is particularly relevant when considering the epidemiology of allergic disease, which seems to be amplified with subsequent generations. At the population level, allergic sensitization seems to have occurred in waves. The first wave was characterized by allergic rhinitis and asthma in industrialized countries (US, UK, Australia), more than 50 years ago. The second wave is now food allergy. Interestingly, developing countries are currently just seeing the first wave. This implies that factors such as pollution, diet, and lifestyle may be driving epigenetic changes in different parts of

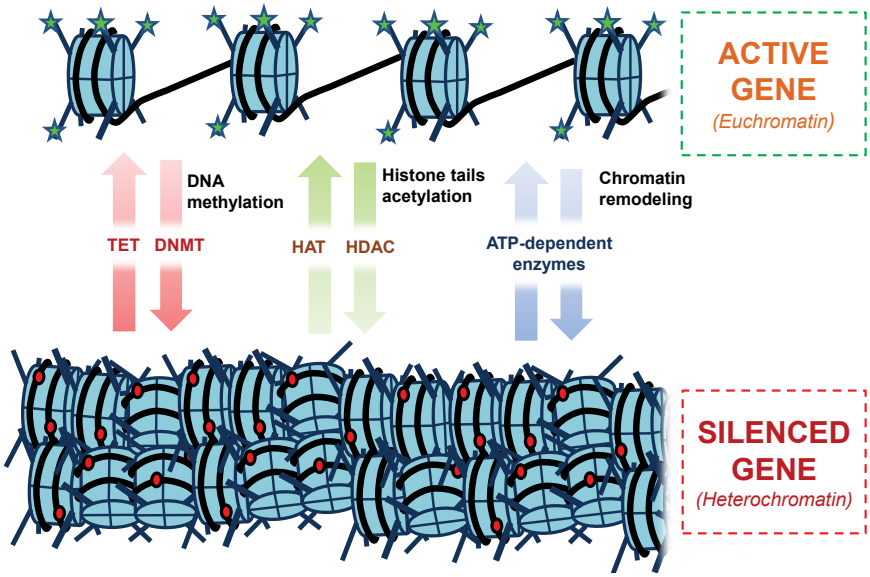

Figure 1 Different epigenetic mechanisms determine a gene's active vs silenced state. DNA methylation involves adding a methyl group DNA base cytosine (red circle). This prevents gene access to transcription factors and promotes other epigenetic changes. Histones, which are large molecules that act as a scaffold for DNA strands, can be modified on their tails. Modification such as histone acetylation (green stars) can favour histone molecules to spread apart, allowing for an open DNA structure called euchromatin. Other histone modifications have been shown to favour a very condensed state (heterochromatin) in which DNA transcription is impossible. Chromatin remodelling is an active process that requires the intervention of various ATP-dependent enzymes. (HAT = Histone acetyltransferase; TET = Ten-eleven translocation dioxygenase; DNMT = DNA methyltransferase; HDAC = Histone deacetylase).

the world that are skewing people towards an allergic phenotype.

Epigenetics is an exciting and expanding field of asthma and allergy research that provides new insight into our understanding of these complex syndromes, and possibly useful biomarkers for diagnosis and characterization of various allergic sub-phenotypes.

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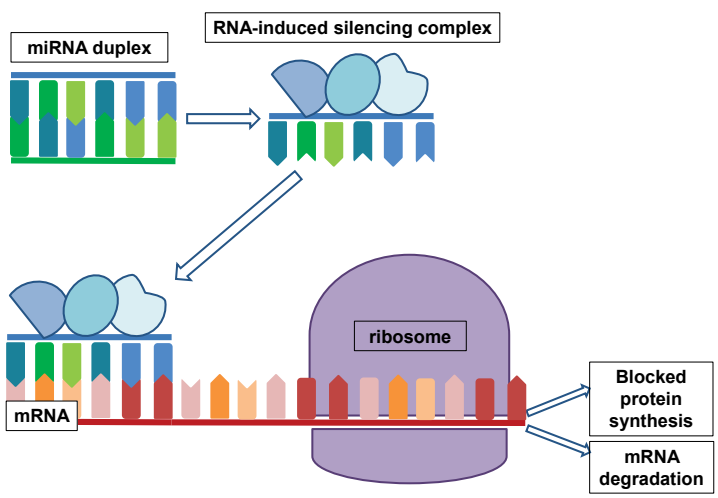

Figure 2 MicroRNA (miRNA) is transcribed from eukaryotic DNA with RNA polymerase to form a double-stranded structure. Further processing of the miRNA results in a structure with other proteins essential to miRNA's function, shown here as the three blue geometric shapes. This complex is called an RNA-induced silencing complex, or RISC. The RISC will bind to complementary mRNA sequences and has 2 modes of action: one, it can occlude and prevent translation of the mRNA into functional proteins; two, it can recruit other proteins to degrade the bound mRNA.

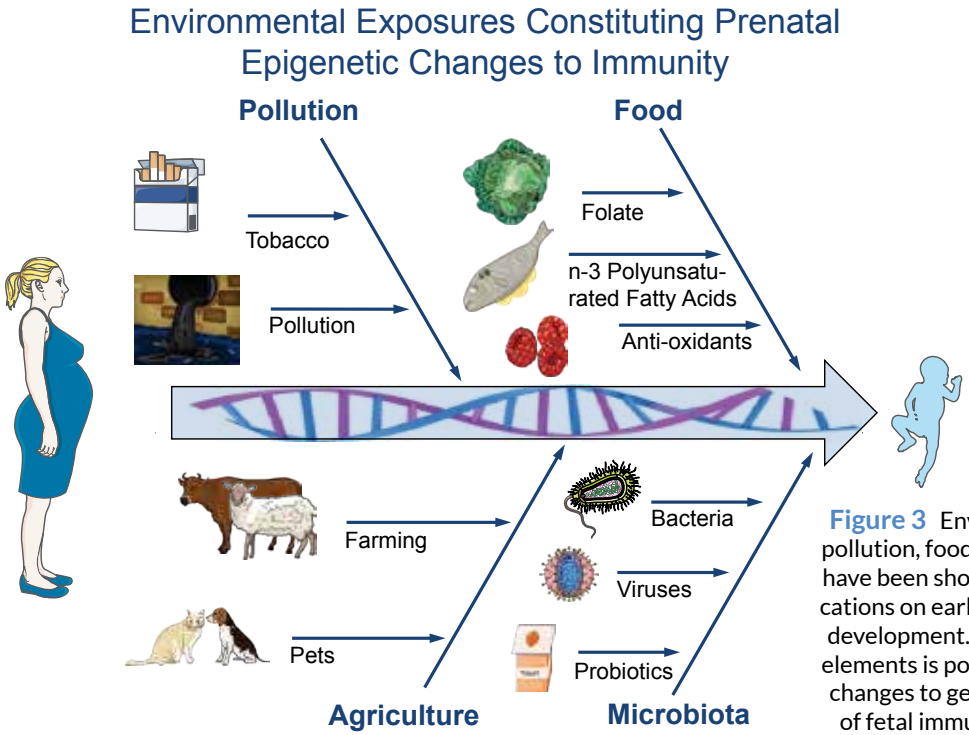

Figure 3 Environmental factors such as pollution, food, agriculture and microbiota have been shown to have significant implications on early immune programming and development. Prenatal exposure to these elements is postulated to cause epigenetic changes to genes and signaling pathways of fetal immunity that may have lasting effects during the child's life.

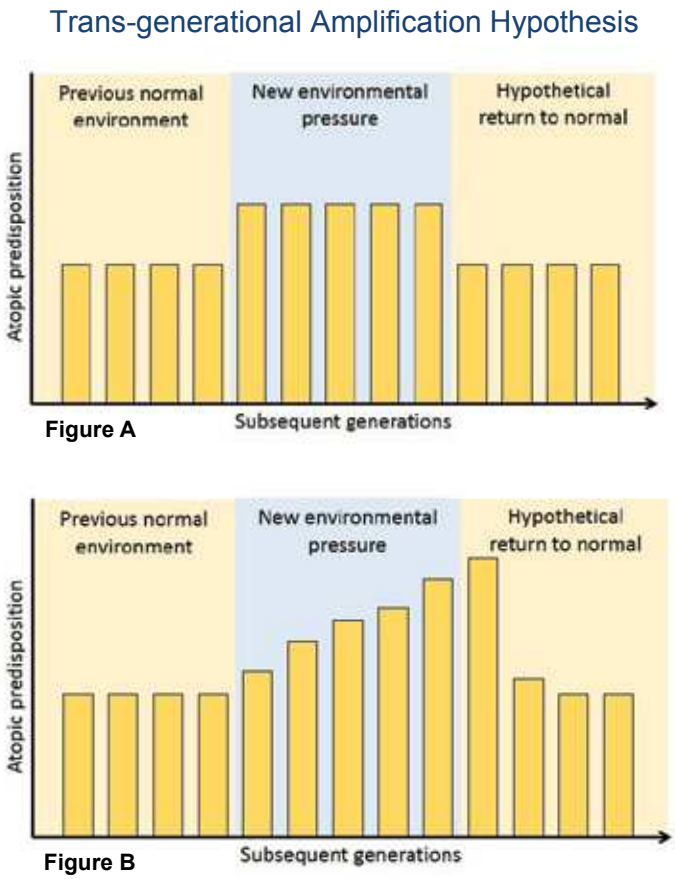

Figure 4 Figure A depicts a trans-generational model of atopic disease predisposition that is solely based on environmental stressors. This model predicts that environmental pressure directly correlates with an increase in baseline genetic risk for disease only for generations that lived during the changed environment. Figure B illustrates an epigenetic transgenerational inheritance model wherein a change in environment not only increases baseline risk for disease but also induces epigenetic changes in subsequent generations as shown in animal models. This could lead to an amplification of the atopic disease that lasts up to two generations after return to normal environment.

28 ENDOTYPES OF ALLERGIC DISEASES

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KEY MESSAGES

- The heterogeneity of allergic diseases in relation to clinically significant outcomes, including response to treatment, pushed towards the development of the concept of phenotypes and endotypes
- There are several benefits of using endotypes such as stratified treatment and better characterization of subjects in genetic and epidemiologic studies and clinical trials for drug development
- Several endotypes can be described for asthma, rhinitis and chronic rhinosinusitis based on the mechanisms of inflammation, driving cause, genetic factors, tissue-related factors and response to treatment
- Translation of biomarkers into pathway-specific diagnostic tests is essential and should guide the design of future clinical trials, incorporating both longitudinal and mechanism-tailored endpoints
- Stratified treatment should be endotype-, biomarker- and outcome-driven

The heterogeneity of allergic diseases in relation to clinically significant outcomes, including response to treatment, has been established beyond any doubt. However, current guidelines ignore disease heterogeneity and causal pathways, leading to unsuccessful clinical "bulk" trials or contradictory results in epidemiologic and genetic surveys.

In the beginning, disease phenotypes describing clinical and morphologic characteristics as well as unique responses to treatment have been developed to address the complexities of the disease. Phenotypes are clinically relevant observable characteristics in terms of presentation, triggers, and treatment response, but do not necessarily relate to or give insights into the underlying pathological mechanism. For most of the allergic diseases heterogeneous and mechanisms of the disease-related metabolic, inflammatory, immunological, and remodeling pathways have been described, and defined as a disease endotype.

There are several benefits of endotyping in a clinical setting (Figure 1). In addition, aligning mouse models to human endotypes is a more relevant approach to the understanding of pathophysiological mechanisms of allergic disease.

New and expensive biological therapies for allergic diseases are emerging that are highly efficacious only for a selected group of patients. The response to targeted interventions in allergic disease may vary among individuals or for the same individual in relation to outcome measures (dissociated effect). Therefore, targeted treatment should be both biomarker-driven and outcome-driven (Figure 2).

The ideal biomarker should be pathway-specific, reproducible, easily measurable, and affordable. Biomarker research is increasingly shifting towards multidimensional approaches, in which the clinical value of a combination of various markers is studied. Translation of biomarkers into pathway-specific diagnostic tests is essential and should guide the design of future large clinical trials, incorporating both longitudinal and mechanism

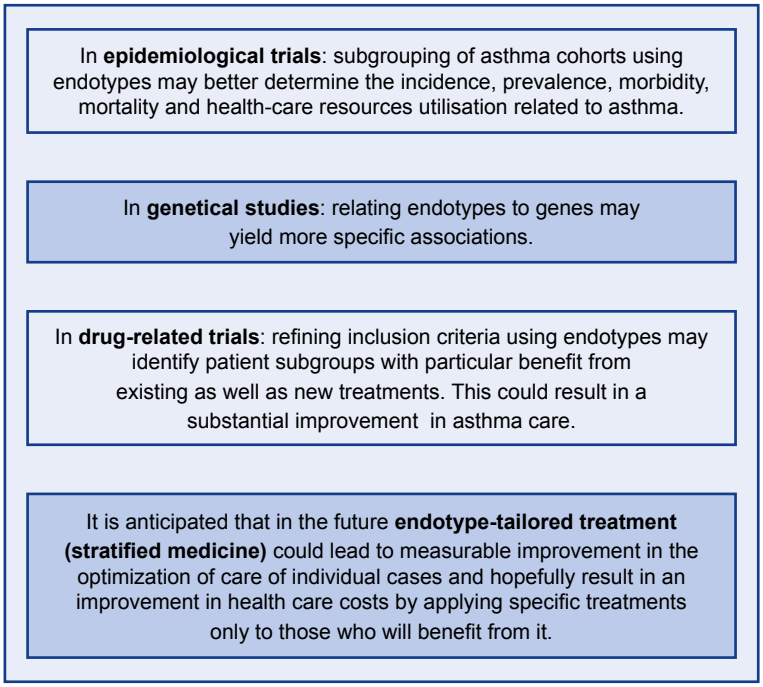

Figure 1 Potential advantages of endotyping. (*Reproduced with permission from Agache I, Akdis C, Jutel M, Virchow JC, Untangling asthma phenotypes and endotypes. Allergy. 2012;67:835-46, with permission from Willey Blackwell.*)

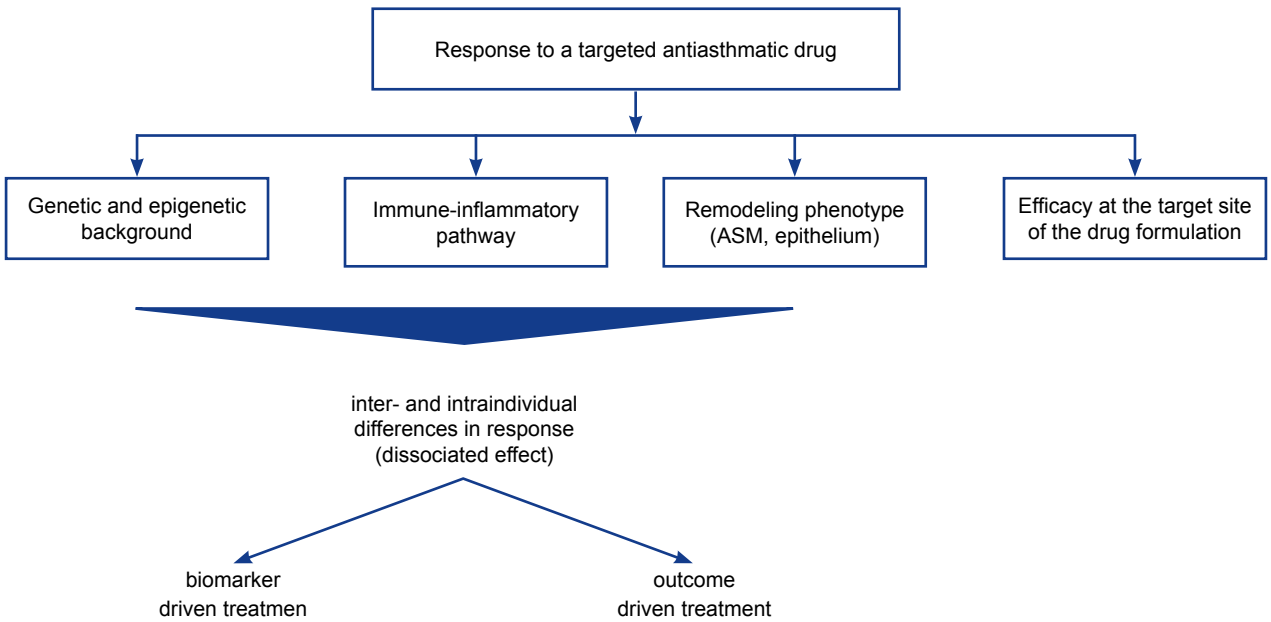

Figure 2 Response to targeted treatment in asthma. (*Reproduced from Agache IO. From phenotypes to endotypes to asthma treatment. Curr Opin Allergy Clin Immunol. 2013 Jun;13:249-56.*)

TABLE 1

Th2 high and Th2 low asthma endotypes

Endotype		Biomarker
Th2 high	IgE driven (atopic and non-atopic)	Total serum IgE IgE on DC Sputum total or specific IgE
	IL-4/IL-13 driven	Serum periostin Sputum IL-13 IL-4 rc α SNPs
	IL-5/eotaxin driven	Sputum/blood eosinophils FeNO Eotaxin 2
	PGD2 driven	?
	Aspirin intolerant	Sputum/urine leukotrienes and prostaglandins
	Mast cell/IL-9 driven)	?
	Eosinophilic obese asthma	Sputum IL-5 Submucosal eosinophils
	Asthmatic granulomatosis (Th1 driven)	Eosinophilic inflammation Corticosteroid resistance ? Autoimmunity markers
	Innate immune response driven	TSLP IL-33/ST-2
Th2 low	Neutrophilic (Th17/ IL-8/purinergic inflammation driven)	Sputum neutrophilia Low IgE Low eosinophils High reversibility
	Paucigranulocytic (EMTU driven)	No inflammation (sputum/bronchial biopsies) Prominent remodeling
	Small airways disease	Flow, resistance, ventilation heterogeneity Alveolar inflammation
	Microbioma	Non-eosinophilic exacerbation-prone asthma PCR evidence of infections
	Innate IR driven	BAL/sputum TNF-α
	Non-eosinophilic obese asthma	L-Arg/ADMA

Abbreviations:

ADMA = asymmetric dimethyl arginine; BAL = broncho-alveolar lavage; EMTU = epithelium-mesenchyme trophic unit; FeNO = fractional exhaled nitric oxide; L-Arg = L-arginine; PCR = polymerase chain reaction; SNPs = single-nucleotide polymorphisms

tailored endpoints. The selection of outcome measures is difficult, as it must reflect the mechanistic intervention and should be relevant for both the population as a whole and for the particular individual.

While endotype-driven therapeutic strategies are becoming increasingly successful in asthma, only feeble attends were made for other allergic diseases. In addition, the issues related to the dissociated effect and drug efficacy at the target site remain unresolved.

For **asthma** the "Th2 high" and "Th2 low" endotypes are well recognized and used to ascribe specific treatment. Several subtypes of the Th2-high and Th2-low endotypes can be described based on the main operating molecular mechanism (Table 1).

Applying the same model to **allergic and non-allergic rhinitis** could prove as successful in promoting personalized approaches, especially for the severe forms of the disease. The well recognized link between rhinitis and asthma should be integrated and tackled within the framework provided by endotypes.

Rhinitis endotypes can be defined in relation to the background inflammation or in terms of treatment responsiveness. The following endotypes can be proposed for allergic rhinitis: eosinophilic or Th2 (IL-4/IL-13) inflammation; steroid-responsive, anti IgE responsive, anti IL-5 responsive, anti IL-4/IL-13 responsive. For non-allergic rhinitis the definition of endotypes (eosinophilic or neutrophilic inflammation, steroid responsive or resistant) should include the driving cause: superantigens, local IgE production, autoantibodies. In the same line a

PRACTALL document described several endotypes for chronic rhinosinusitis (CRS) characterized by differences in responsiveness to treatment, including topical intranasal corticosteroids and biological agents, such as anti–IL-5 and anti-IgE mAb (Figure 2). Some of the described CRS endotypes were based on different biomarkers linked to underlying mechanisms.

Atopic dermatitis (AD) is a chronic inflammatory skin disease with complex genetic and immunological mechanisms. Several endotypes can be proposed according to the inflammatory background such as Th2/IL-22/periostin high or Th17/Th1 high or in relation to the expression of fillagrin, MATT or vitamin D pathway genes mutations. For the Th2 type AD serum periostin is related to disease severity. Targeting both the inflammatory-immune dysregulated pathways or the barrier defect holds future promise. Several new targets such as toll-like receptors, type 2 innate lymphoid cells and tight junction proteins are emerging. Promising new therapeutic agents in the near future are sphinganin, cannabinoids and highly targeted monoclonal antibodies.

For **food allergy** phenotypes prove useful for predicting severe reactions. Different phenotypes of children with cow's milk allergy can be distinguished by casein- and milk-specific IgE levels, milk specific basophil reactivity, and milk SPT mean wheal diameters. In another study IL-25 was found highly elevated only in children with a clinical response to peanut, suggesting a role for IL-25 in the pathogenesis of peanut allergy and as a biomarker of a severe atopic phenotype.

For **drug allergy** several phenotypes were described for the hypersensivity to non-steroidal anti-inflammatory drugs (NSAIDS): aspirin-exacerbated respiratory disease, aspirin-exacerbated cutaneous disease, multiple NSAID-induced urticaria/angioedema, single NSAID-IgE reactions and single NSAID T cell responses, which differ in terms of the pathogenic pathways involved, as well as the mediators released after provocation tests.

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29 ANIMAL MODELS OF ALLERGIC DISEASE

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KEY MESSAGES

- A wide range of animal models exist for a variety of allergic diseases
- Animal models are particularly useful for identifying novel cellular and molecular immunological mechanisms of allergy
- No single animal model completely recreates all the aspects of an allergic response

Animal models have been developed for almost all types of allergic disease such as asthma, allergic rhinitis, food allergy, anaphylaxis, atopic dermatitis and allergic conjunctivitis. These models are important to examine the mechanism of the disease, the activity of a variety of genes and cellular pathways, define the role of environmental factors (such as the microbiota), predict the safety of new drugs before being used in clinical studies, define the pathogenic pathways and suggest new therapeutic options. The correct animal model should reflect the disease pathophysiology as closely as possible and new models are essential for the development of new therapies.

Laboratory mice do not usually spontaneously develop allergies and a range of sensitization and challenge protocols have been developed. The number of sensitizations and challenges is decisive for the development of acute or chronic forms of these models. The nature of the allergic disease and inflammatory response is directly influenced by the genetic background of the mice, the allergen, type of the sensitization and challenge protocol and contamination of the allergen with substances (e.g. LPS), which stimulate the innate immune response. Certain protocols require the combination of allergen with an adjuvant, for example aluminium hydroxide (ALOH3, Alum), which is one of the preferred adjuvants in respiratory allergy models. The sensitization, challenge and analysis parameters of murine allergy models are summarized in Figure 1.

Although murine models of allergy provide important insights into the disease mechanisms, there are some limitations that should be considered. In addition to the genetic and physiological differences between humans and mice, there are also limitations due to complexity of this disease. In other words, mice do not develop allergy. One can replicate important components of the disease, but no single model accurately models all the features of allergy. This is very important to take into account when choosing the correct model to address the specific experimental question. For example, chronic exposure models are required to examine many of the structural changes associated with allergic responses within the airways.

Notwithstanding the limitations of these models, several studies carried out in animal models have given important clues that explain the pathophysiological conditions related to the disease status. For instance, the role of Th2 type cytokines and T regulatory cells in the pathogenesis of allergy have been particularly well-studied in animal models.

Human clinical studies remain the gold standard for determining the clinical efficacy of new therapeutic approaches. Murine models

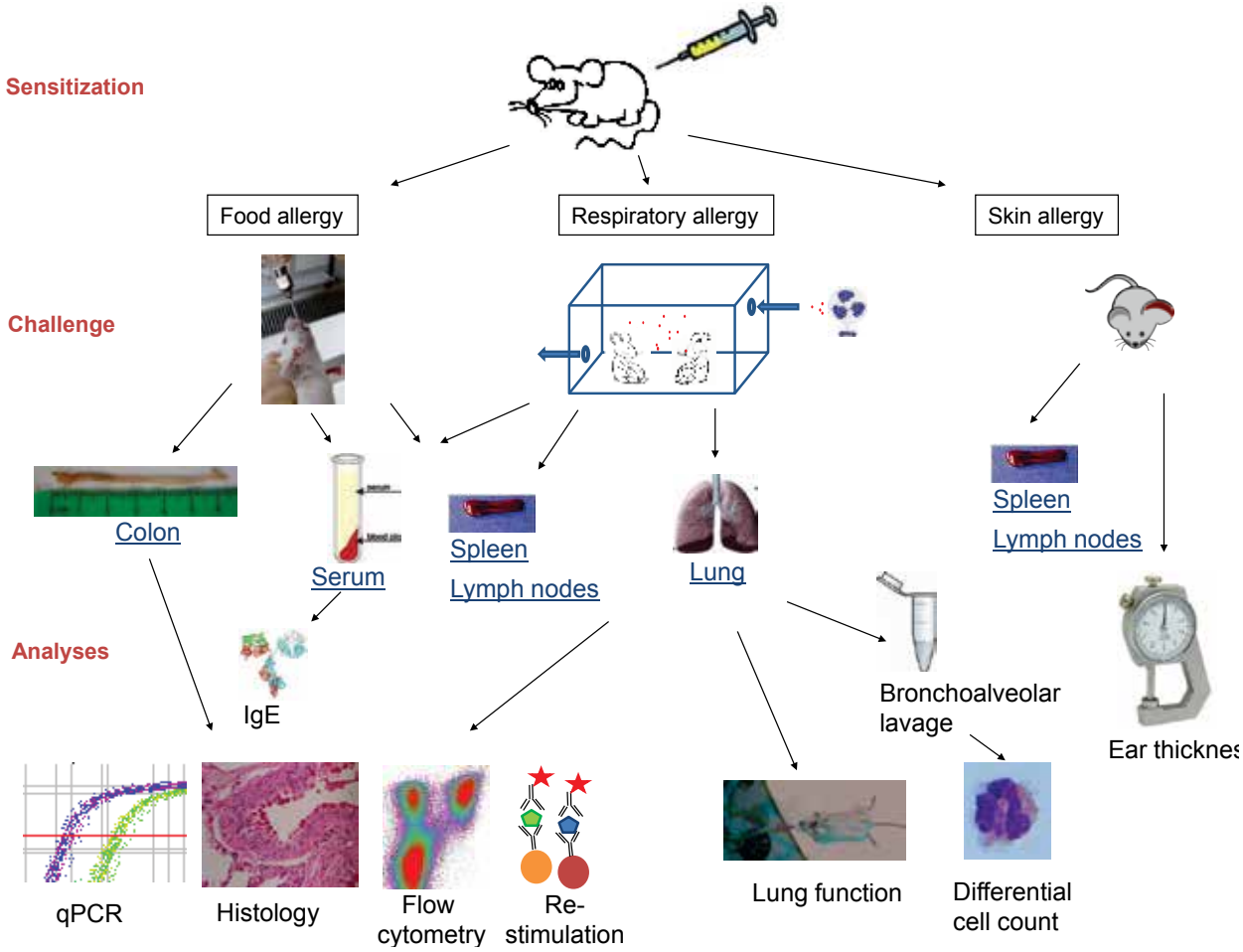

Figure 1 Overview of the experimental steps commonly used in allergy models. Allergy mouse models typically comprise a sensitization, a challenge, and an analyses phase. After sensitization, allergic responses are provoked, depending on the model, by oral application (food allergy), by inhalation (respiratory allergy), or by skin contact (skin allergy) with the allergen. The severity and mechanisms of the allergic response are determined using a variety of technologies, focused on the relevant model organs or using functional assessments such as lung function testing or ear thickness measurements.

will continue to provide important mechanistic clues, while improved models may extend our understanding of the basic mechanisms for examining new therapeutic options.

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Section B

EPIDEMIOLOGY AND RISK FACTORS

* The allergy epidemic
* Natural history of allergy
* Birth cohorts
* Environmental risk factors for allergy: outdoor/ indoor pollution and climate change
* Measuring exposure to environmental airborne allergens
* Environmental risk factors for allergy: food
* Environmental risk factors for asthma: home environment
* Environmental risk factors for allergy: working environment
* Risk factors for childhood asthma: viral infection and allergic sensitization
* Environmental risk factors for allergy: helminth infections
* Perinatal immune development and its role in atopy development
* Perinatal risk and protective factors for allergic diseases
* The role of microbiome

1 THE ALLERGY EPIDEMIC

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KEY MESSAGES

- In countries undergoing the epidemiological transition phase, allergies appear first among the richest, but soon affect the middle class and finally the disadvantaged
- Food allergies are emerging as a "second wave" of the allergy epidemic and they persist more frequently
- Epidemiological studies suggest that a high "*antigenic burden*" in early life, provided by infections and nutrition, can properly "educate" the immune system and prevent childhood allergic diseases
- A reduced "antigenic burden" implies a reduced stimulation of the immune system and contributes, in genetically predisposed individuals, to dysregulated immune response leading to allergy
- The discovery of the lifestyle factors promoting allergy susceptibility will inspire primary prevention strategies to revert the allergy epidemic trend

The growing worldwide burden of allergic rhinitis, asthma and atopic eczema has been properly defined as the "allergy epidemic". During the last two centuries, this phenomenon has characterized countries undergoing their epidemiological transition phase. Respiratory allergies (allergic rhinitis and asthma) appeared first among the richest, then spread within the middle class and finally affected also the disadvantaged. Following a similar pattern, respiratory allergies and atopic eczema are nowadays on the rise in middle income countries, especially in the urban areas (Figure 1).

More recently, food allergies are clearly becoming more prevalent in westernized populations (Figure 2). This "second wave" of the allergy epidemic is already generating a heavy burden on health systems not well prepared to face this new challenge. The increasing prevalence of food allergies is associated with fatal anaphylaxis in children and adolescents.

A decline of microbial diversity was proposed since the late nineties as a major cause of the allergy epidemic. This area of the hygiene hypothesis, now defined "*biodiversity hypothesis*", has found specific support in several epidemiological studies: 1) respiratory allergies are inversely related to the number of different foodborne infections; 2) a lower diversity of the gut microbial flora in the first week of life is associated with atopic eczema at 18 months (Figure 3); 3) the probability of developing asthma in farming children is inversely related to the range of exposure to environmental bacteria and fungi.

Two recent studies have coherently shown that reduced food diversity in infants' diet is associated with atopic sensitization and allergic diseases later in childhood (Figure 4). A sufficiently high "*antigenic burden*" in early life, provided by infections and nutrition, is therefore necessary to properly "educate" the immune system and to prevent childhood allergic diseases.

Current knowledge is a good basis to identify the allergy protective factors and to inspire primary and secondary prevention strategies to revert the allergy epidemic trend. Allergy prevention based on the administration of probiotics to pregnant mothers and to in-

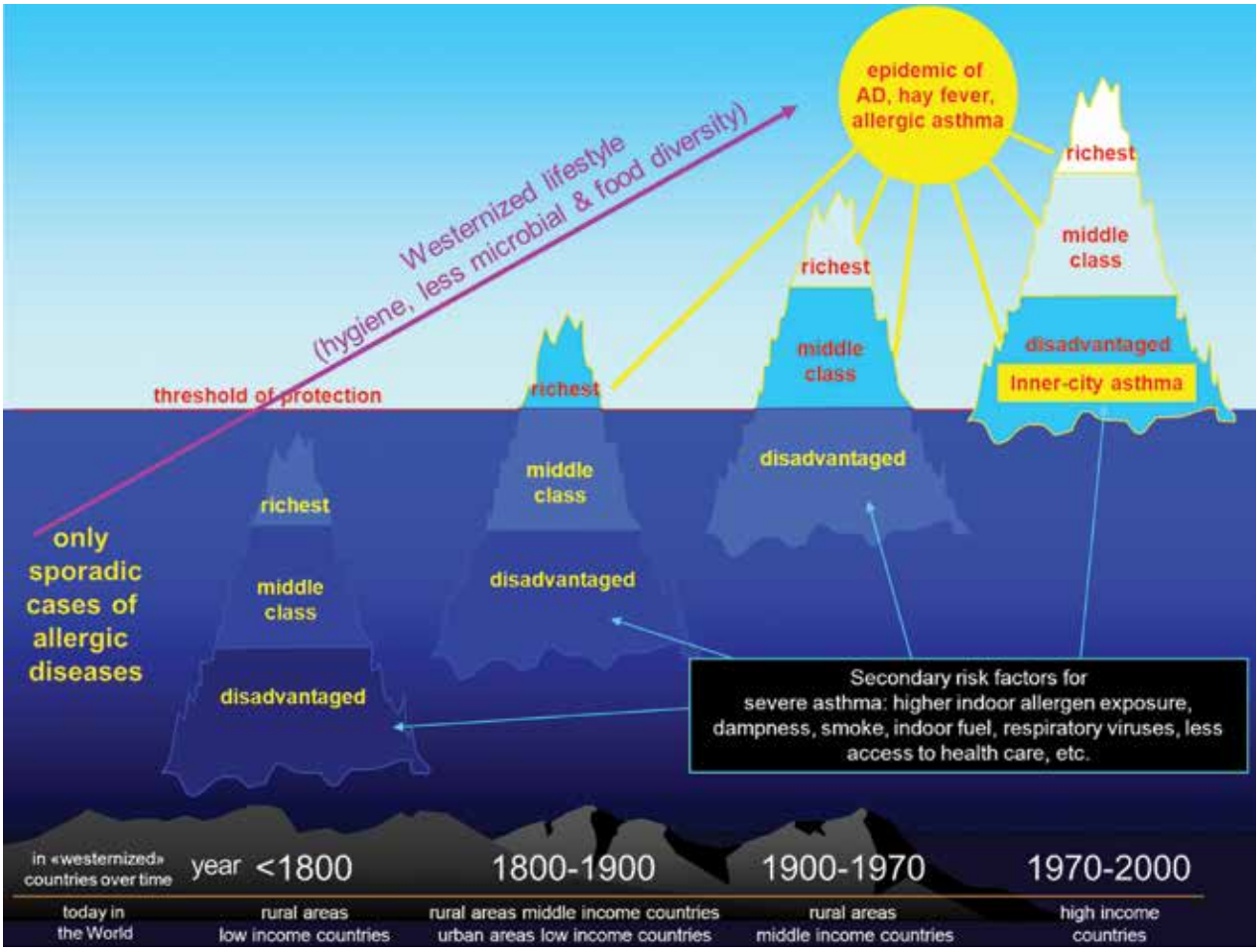

Figure 1 The spread of hay fever and allergic asthma according to socio-economic status and westernization level. (*Reproduced with permission from Annals of Allergy, Asthma & Immunology, Vol. 89(S1). Matricardi PM, Bouygue GR, Tripodi S. Inner-city asthma and the hygiene hypothesis, 69–74. Copyright Elsevier 2002.*)

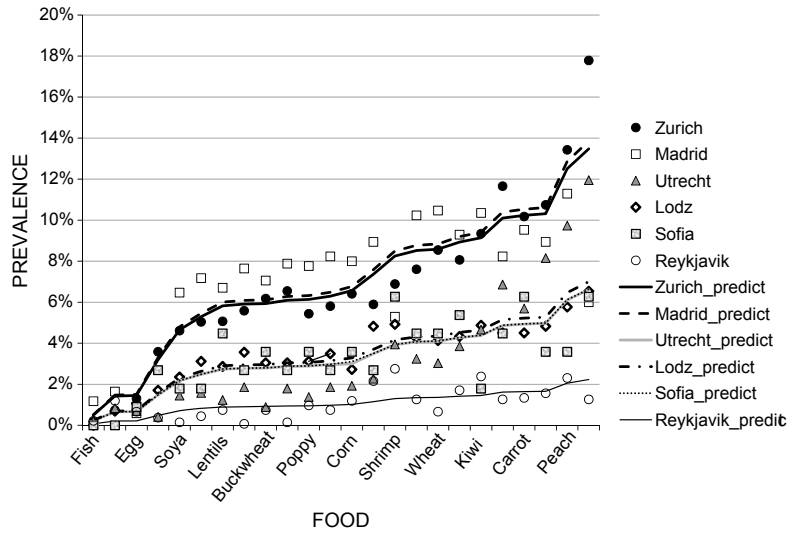

Figure 2 Observed and predicted values for the prevalence of food IgE sensitization in 20- to 54-year-olds in European cities. (reprinted from Allergy, Vol. 69. Burney PGJ et al. The prevalence of food sensitization among European adults. pp. 365–71. Copyright 2014 (*Reproduced with permission from Burney PGJ, Potts J, Kummeling I, et al. The prevalence of food sensitization among European adults. Allergy, 2014 69: 365–71, with permission from Willey Blackwell.*)

fants provided unfortunately conflicting and still debated results. Other strategies under investigation include the safe administration of oral or intranasal bacterial extracts and earlier introduction of foods.

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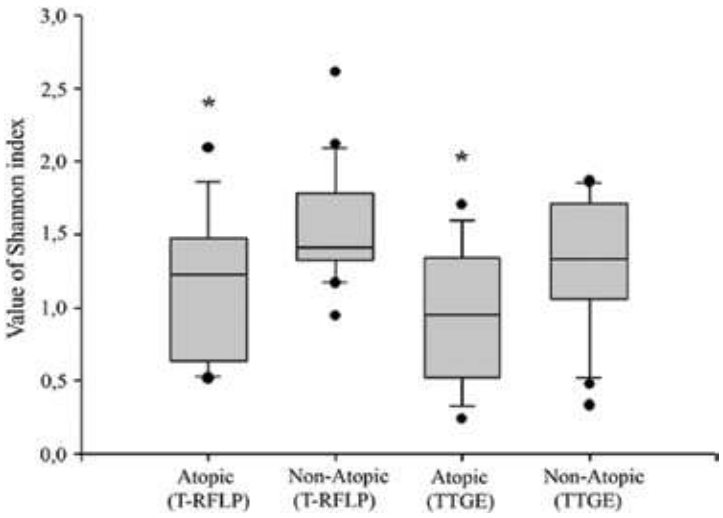

Figure 3 Shannon-Wiener index after T-RFLP of 16S rDNA with AluI for cutting and TTGE, respectively, generated from the fecal microbiota of 1-week-old infants that at 18 months had atopic eczema or stayed healthy. For each group, median and 10th, 25th, 75th, and 90th percentiles are shown. *For T-RFLP, P<.01 and for TTGE, P<.05 (*Reprinted from J Allergy Clin Immunol, 121/1, Wang M, Karlsson C, Olsson C, et al. Reduced diversity in the early fecal microbiota of infants with atopic eczema, 129-134, Copyright 2008, with permission from Elsevier.*)

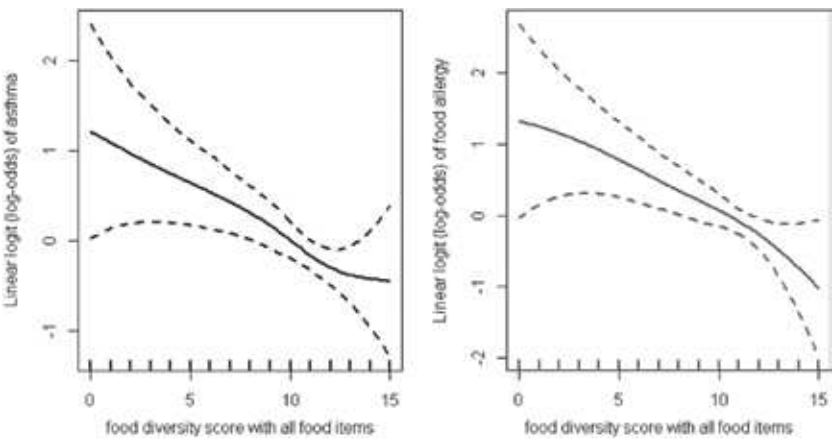

Figure 4 Association of increasing diversity of food introduced within the first year of life with (A) asthma and (B) food allergy among 856 children who participated in a birth cohort study, Protection Against Allergy Study in Rural Environments/EFRAIM. The figure shows the diversity score with all different food items for the entire study population. The solid lines represents the predicted value of (A) asthma or (B) food allergy, as a function of the score, and dashed lines represent the corresponding CI. The y-axis is the linear logit of (A) asthma or (B) food allergy, and the values are centered on 0 (50/50 odds) and extended to both positive and negative values. All models are adjusted for farmer, center, duration of breast-feeding, parents with allergy, maternal education, sex, and siblings. (*Reprinted from J Allergy Clin Immunol, 133/4, Roduit C, Frei R, Depner M et al. Increased food diversity in the first year of life is inversely associated with allergic diseases, 1056-1064, Copyright 2014, with permission from Elsevier.*)

2 NATURAL HISTORY OF ALLERGY

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KEY MESSAGES

- Atopic eczema (dermatitis) is usually the first manifestation of an atopic disease. Not all children with infantile eczema show a sensitisation to food allergens and will develop classical allergy
- Sensitisation to foods precedes sensitisation to inhalant allergens. Persistent sensitisation before and after 3 years of age is a risk factor for school age asthma
- Early infantile eczema, early sensitisation during the first 3 years of life and atopic family history are predictors of allergic airway disease and persistence of asthma until puberty
- Children with infantile eczema often lose their symptoms until school age, although early onset is more frequently associated with persistence until puberty compared to children with later onset of the disease
- Remission of allergic asthma occurs not frequently up to the age of 20 years

Allergy is common in children, adolescents and adults. Epidemiological studies like the German MAS (Multicentre Allergy Study) showed age-related typical manifestations of atopic and allergic diseases. In the "Atopic March" infantile eczema and food allergy precede the onset of allergic airway disease (rhinitis and asthma).

However, there are individuals with isolated allergic airway disease (for example hay fever) starting later in life at school age without any signs of other atopic disease during infancy and preschool age. Equally, there are children with infantile eczema without any signs of food or inhalant allergy. Furthermore, remission and relapse of disease entities are possible at any time.

Studies on the molecular pattern of sensitisation to pollen allergens showed a preclinical phase, where sensitization (IgE antibodies in serum) to certain molecules of an allergen source (grass or birch) precedes symptoms. The likelihood of clinical allergy increases with the number of molecules recognized by IgE.

ATOPIC ECZEMA

The incidence of atopic eczema and food allergy to cow`s milk, hen`s egg, wheat and soy is highest during the first 2 years of life in childhood, however, there is a second peak of new onset of atopic eczema in puberty for females. Two third of young children with infantile eczema will lose their symptoms up to the age of three years. However, those children developing atopic eczema later in life (after the age of 5 years) are more likely to outgrow their eczema compared to those children, who had an earlier onset of disease (during the first year of life).

ASTHMA

In the German MAS cohort, the prevalence of asthma is 4% at 6 years of age and more prevalent in boys and 9% at age 20 years. The incidence of allergic asthma is highest during preschool and early school age (Figure 1). There is a second peak for new onset of asthma in females at puberty. Atopic family history is a major risk factor for the development of asthma (Figure 2). 29% of the German MAS cohort children with complete follow-up showed wheezing episodes during the

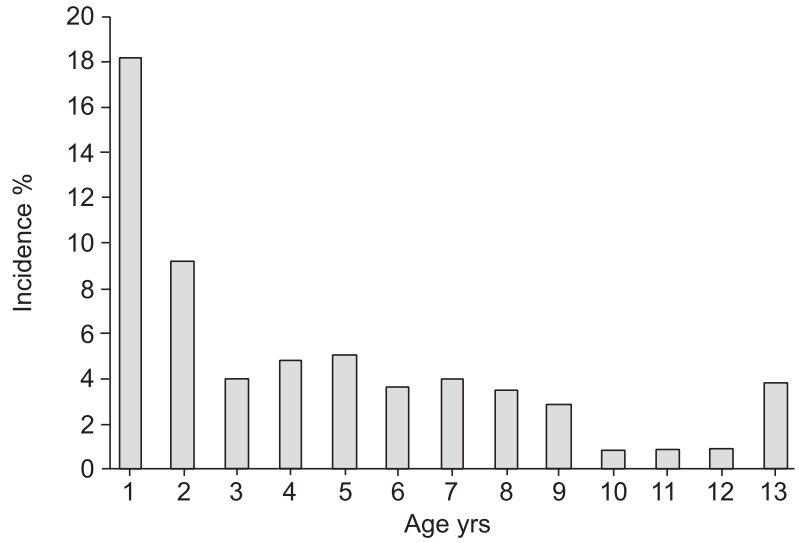

Figure 1 Incidence of asthma in the German MAS cohort. (*From Matricardi PM, Illi S, Grüber C,et al. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. Eur Resp J 2008; 32:585-92; Reprinted with permission under the Creative Common Attribution License or equivalent.*)

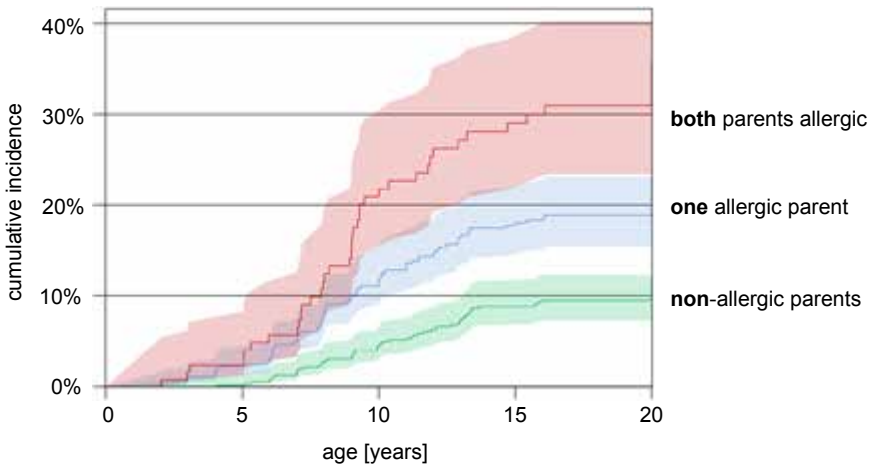

Figure 2 Family history for asthma and cumulative incidence of allergic diseases in offsprings. (*Reprinted from J Allergy Clin Immunol, 133/4, Grabenhenrich LB, Gough H, Reich A, et al. Early-life determinants of asthma from birth to age 20 years: A German birth cohort study, 979-988, Copyright 2014, with permission from Elsevier.*)

first three years of life (early wheezers). 9% started wheezing between the age of 3 to 6 years (late wheezers) and another 9% started wheezing after 6 years of age (very late wheezers). Early persistent wheezers (early start of wheezing before 3 years of age, wheezing also after 6 years of age) showed the highest rates of atopy. In this group, early atopic eczema, parental atopy and early sensitization (<3 years of age), especially to perennial allergens, turned out to be the major risk factors for persistence of asthma/wheeze at age 11-13 years.

IGE SENSITISATION TO ALLERGENS

The first allergens recognized by the immune system in terms of IgE production are food allergens. The most frequent food allergens inducing IgE-mediated sensitization are hen`s egg, cow`s milk and peanut. Although, sensitisation to inhalant allergens like cat, house dust mite and pollen allergens can be present already during the first 3 years of life, in most of the children the clinical relevance is observed later, at school age.

Atopy (sensitisation) in general is a risk factor for asthma at school age (Figure 3).

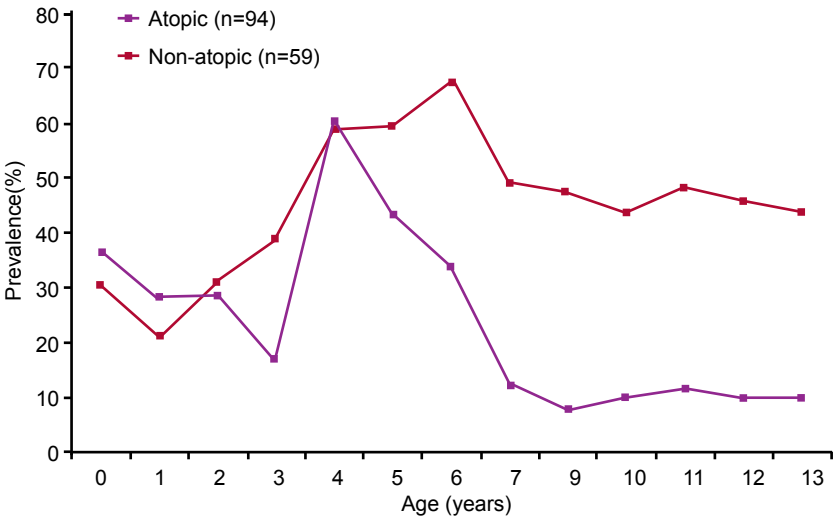

Figure 3 Prevalence of current wheeze from birth to age 13 years in children with any wheezing episode at schoolage (5-7 years) stratified for atopy at school age. (*Reprinted from The Lancet, 368, Illi S, von Mutius E, Lau S, et al, Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study, 763-770, Copyright 2006, with permission from Elsevier.*)

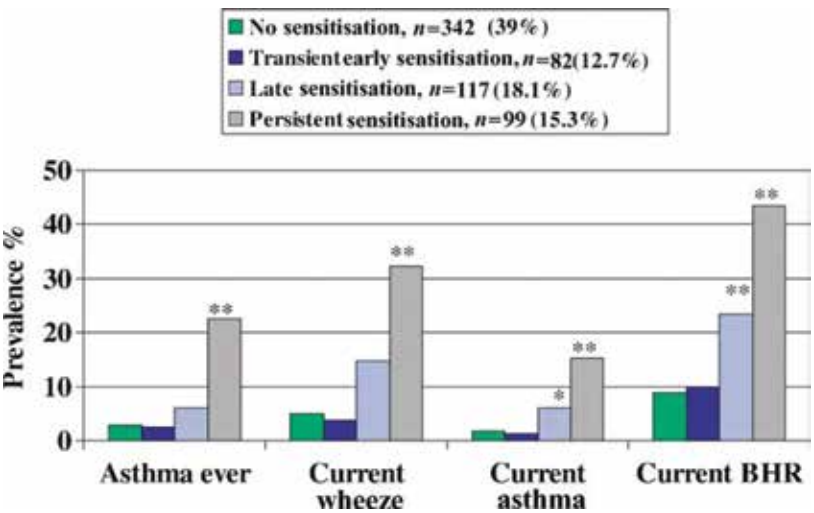

Figure 4 Prevalence of asthma and asthmatic symptoms at 7 years of age, stratified for sensitization patterns and bronchial hyper-responsiveness (BHR). * p< 0.05; ** p<0.001. (*Reprinted from J Allergy Clin Immunol, 108/5, Illi S, von Mutius E, Lau S, et al. The pattern of atopic sensitization is associated with the development of asthma in childhood, 709-714, Copyright 2001, with permission from Elsevier.*)

Sensitisation to indoor allergens (house dust mite and pets) is associated with allergic asthma.

School children with sensitisation to perennial allergens (house dust mite, cat dander) being highly exposed to these allergens early in life are at risk to have impaired lung function at school age compared to children without sensitisation or with sensitisation and low exposure to indoor allergens during the first year of life.

Children with sensitization to any allergen before the age of 3 years and sensitization to inhalant allergens have an increased risk for asthma at school age (Figure 4).

ALLERGIC RHINITIS

There is a constant rise for the incidence and prevalence of allergic rhinitis (AR) from preschool and early school age until puberty.

Allergic rhinitis until the age of 5 years was found to be a risk factor for subsequent wheezing onset with an adjusted relative risk of 3.79 (p<0.001). This association was not attributable to the type of sensitization, the severity of sensitization or atopic dermatitis during the first 2 years of life. On a population level 41.5% (95% CI: 20.0-61.3) of all new cases of wheezing was attributable to preceding AR. Neither AR until the age of 2 years nor non-allergic rhinitis until the age of 5 years were significantly associated with wheezing onset in childhood.

The first manifestation of AR occurs in preschool children, where it is a risk factor for subsequent wheezing onset. Preschool children with rhinitis might thus benefit from early assessment of allergic sensitization to identify the children at high risk of developing wheezing.

ALLERGIC RHINITIS: SENSITISATION TO AERO-ALLERGENS

The 12-month prevalence of sensitization to indoor or outdoor allergens in the German MAS cohort rose with each time point of assessment, reaching almost 60% of all boys and a third of all girls at the age of 13 years (in children with one or two allergic parents). Children from non-allergic parents were less sensitized compared to

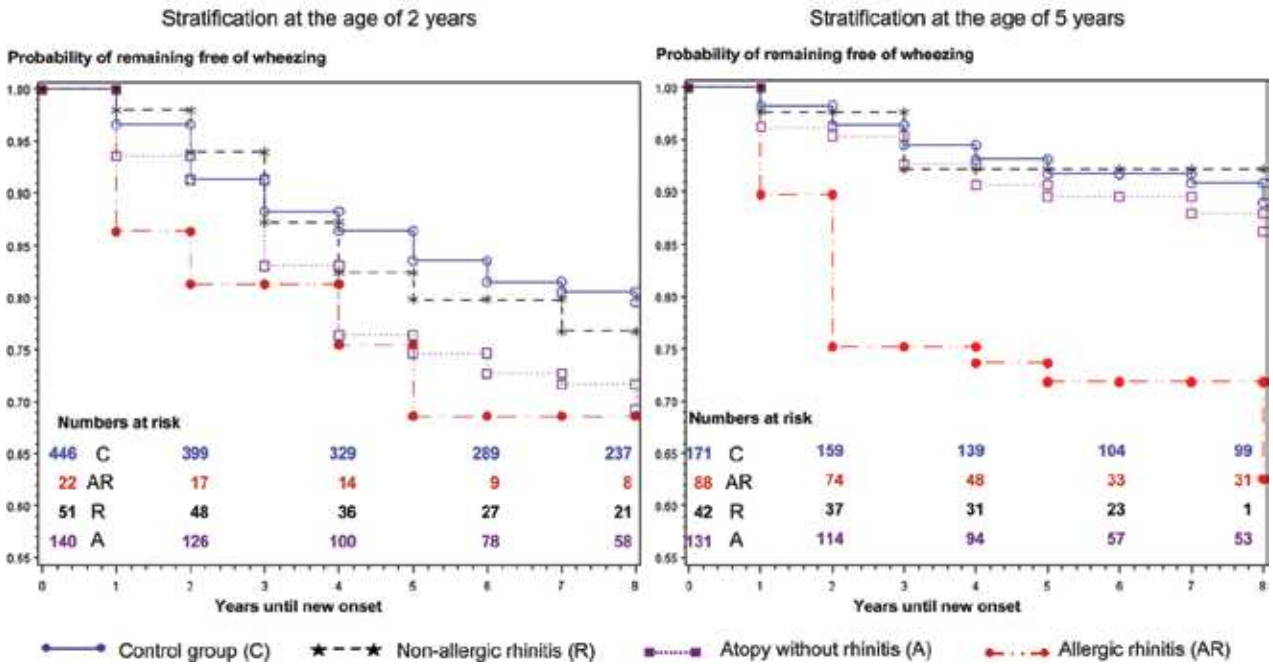

Figure 5 Probability of wheezing onset stratified by the 4 rhinitis phenotypes (allergic rhinitis, non-allergic rhinitis, atopy without rhinitis and control group) .at the ages of 2 and 5 years. (*Reprinted from J Allergy Clin Immunol, 126/6, Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children, 1170-1175, Copyright 2010, with permission from Elsevier.*)

those with allergic parents. Irrespective of parental allergy status the number of boys sensitized to aero-allergens was approximately twice the number of sensitized girls at age 13 years.

At the age of 13 years, 91% out of the 35 children with "severe persistent" AR (ARIA) were sensitized to at least one aero-allergen, whereas this proportion was only 70% among the 56 children with "mild persistent" AR (p=0.015). This difference was similar at the age of 10 years, although overall slightly less children with AR were sensitized (p=0.033). Among the asymptomatic children 18% (32/175) were sensitized to at least one common aero-allergen at the age of 13 years, compared to 24% (49/289) at the previous time point of assessment at the age of 10 years.

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3 BIRTH COHORTS

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KEY MESSAGES

- Allergic diseases generally start early in life, thus birth cohorts are essential for elucidating disease mechanisms and natural course and evidence-based strategies for prevention and management
- Birth cohort studies have been instrumental in demonstrating the existence of a gene-environment interaction in the development of allergy and in identifying children at risk for allergy
- Several consortia (STELAR, MeDALL, EuroPreval/iFAM, EAGLE) bring together a number of ongoing birth cohort studies to facilitate data sharing

In contrast to most other complex diseases (for example diabetes or hypertension), allergic diseases generally start early in life. Therefore, the best way to study allergies is to recruit new born babies and follow them as they grow (so-called birth cohort). Birth cohorts overcome problems related to the lack of accuracy (or completeness) of the recollections when patients are asked about the events, which occurred many years ago. Such studies permit careful longitudinal assessment of symptoms, sensitization status, physician diagnoses and medication usage, and objective measures such as lung function.

Allergies are heritable, but despite lots of effort, we have had limited success identifying what genes are important, and this has yet to impact on patient care. Many factors in the environment contribute to the development of allergies (for example diet, immunizations, antibiotics, pets and tobacco smoke), but we don't know how to modify the environment to reduce the risks. In birth cohorts, environmental exposures can be measured to allow the study of complex gene-environment interactions. Birth cohort studies have been instrumental in demonstrating the existence of a gene-environment interaction in the development of allergy, which helped to explain the disparities in genetic association studies in different settings around the world.

Several consortia bring together a number of ongoing birth cohort studies to facilitate data sharing. For example, the UK Study Team for Early Life Asthma Research (STELAR) brings together the network of all UK-based birth cohorts designed to study allergies with the experts in machine learning and epidemiologically-oriented health informatics. Similarly, EU-funded MeDALL (Mechanisms of the Development of ALLergy)1 and EuroPreval/iFAM2 projects bring together thousands of children taking part in different birth cohorts across the continent, and will facilitate the generation of critically important knowledge on the mechanisms of initiation of allergy. Birth cohorts in The EArly Genetics and Lifecourse Epidemiology (EAGLE) Consortium are extensively collaborating to investigate the genetic basis of allergy and asthma-related phenotypes in childhood.

Numerous early breakthroughs have already been made. The ongoing birth cohort studies offer the best chance of identification of children at increased risk of allergy. This is the first and crucially important step towards the development of the evidence-based strategies for prevention of allergy development, and stratified

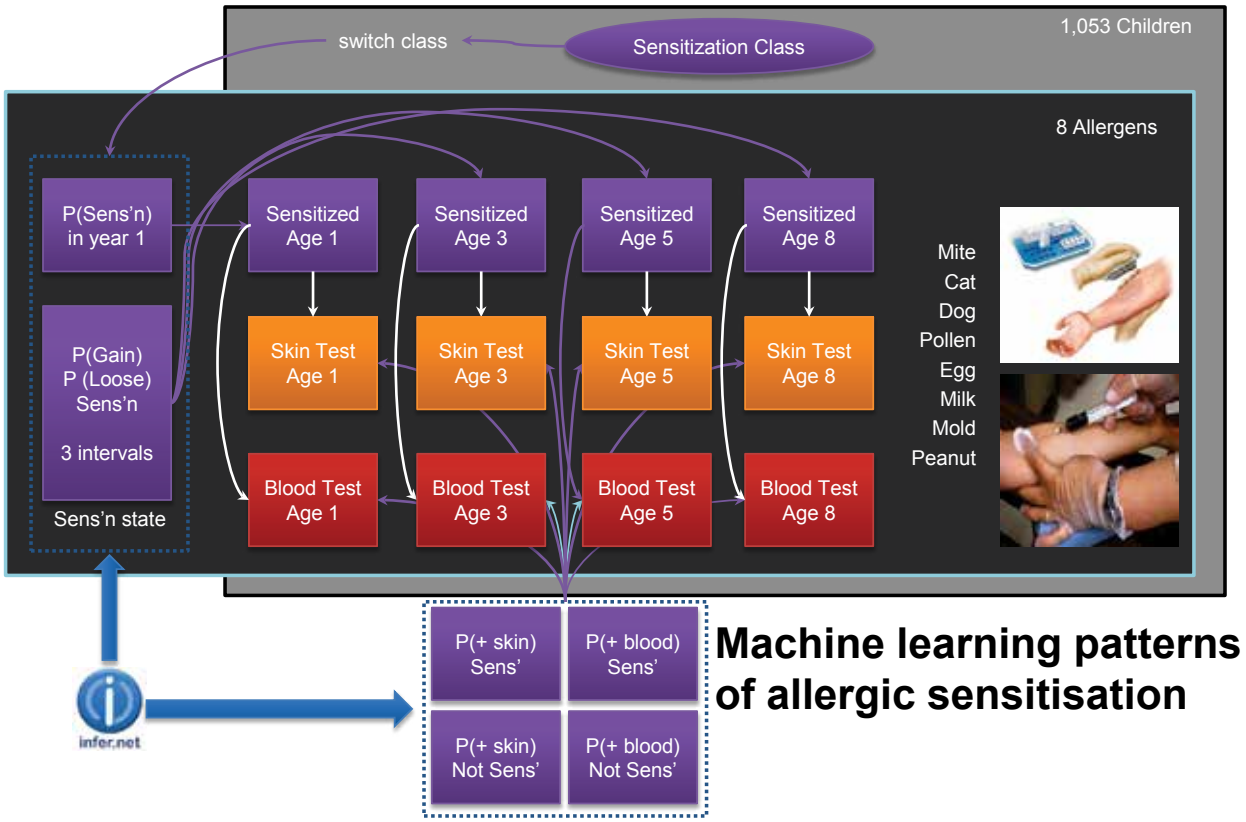

Figure 1 Longitudinal data collected over a number of years in birth cohort studies are a foundation for utilisation of the power of novel state-of the art data analysis techniques to build complex models to describe different types of allergic diseases. In doing so, we will understand the basic biological mechanisms that underlie the different allergies, and identify novel targets for future drug therapies.

(personalised) management of allergies (Figure 1). Existing birth cohorts of individuals now at various ages, from childhood to adulthood, should be considered a treasure, and every effort should be made to maintain long-term funding for such large efforts.

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4a ENVIRONMENTAL RISK FACTORS FOR ALLERGY: OUTDOOR/INDOOR POLLUTION AND CLIMATE CHANGE

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Allergic diseases are a heavy socio-economic burden worldwide. There is a deficit in public awareness, education and training and an urgent need for efficient prevention strategies. The rising trend in allergies has been associated with changes in life-style, such as improved hygiene measures, smaller family sizes and control of infections, which, taken together, result in an "under-challenged" immune system. On the other hand, life-style changes include the exposure to potentially harmful – indoor and outdoor – environmental pollutants suspected to keep our immune system in a constant state of alarm. How does this fit together?

KEY MESSAGES

- Allergy is an environmental disease as the most common and earliest onset chronic non-communicable disease
- Life-style and civilization related risk factors for allergy are encountered both indoors and outdoors
- Allergy-relevant indoor air pollutants include environmental tobacco smoke and volatile organic compounds
- Anthropogenic environmental factors influence pollen allergenicity indirectly via their effects on pollen-producing plants
- Climate change-related effects contribute to an increased allergen burden in outdoor air
- The growing evidence of man-made environmental risk factors for allergy highlights the importance of prevention strategies for improving public health

INDOOR RISK FACTORS

In the western civilization, most individuals spend a considerable part of their lives indoors. Indoor exposure to mite, molds, chemicals and inhaled particles can elicit and/or exacerbate allergic diseases. The best assessed among the indoor pollutants are volatile organic compounds (VOCs) and environmental tobacco smoke (ETS), which is a mixture of VOCs, carbon monoxide and solid particles. In LINA (Lifestyle and environmental factors and their Influence on Newborns Allergy risk) birth cohort subgroup, prenatal and early life exposure to environmental tobacco smoke was positively correlated with circulating eosinophil and basophil precursors in cord blood, indicating allergy-promoting effects on susceptible children. In a murine allergic asthma model, long-term exposure to VOCs emitted from polyvinylchloride (PVC) flooring increased acute and chronic allergic lung inflammation.

OUTDOOR RISK FACTORS

A high degree of traffic and urbanization are hallmarks of Western civilization. A recent meta-analysis of prospective, multi-center trials did not find any clear association of modeled traffic-related air pollution and allergic sensitization in children (Figures 1 and 2). Other studies do show associations of exposure to diesel exhaust particles (DEP), NO2, ozone and particulate matter (PM), with asthma, allergic rhinitis or sensitization to aeroallergens. These conflicting results illustrate how exposure and confounding factors, e.g. genetic predisposition, lifestyle and nutrition interact closely in switching from health to disease (Figure 3). Apart from direct effects of outdoor pol-

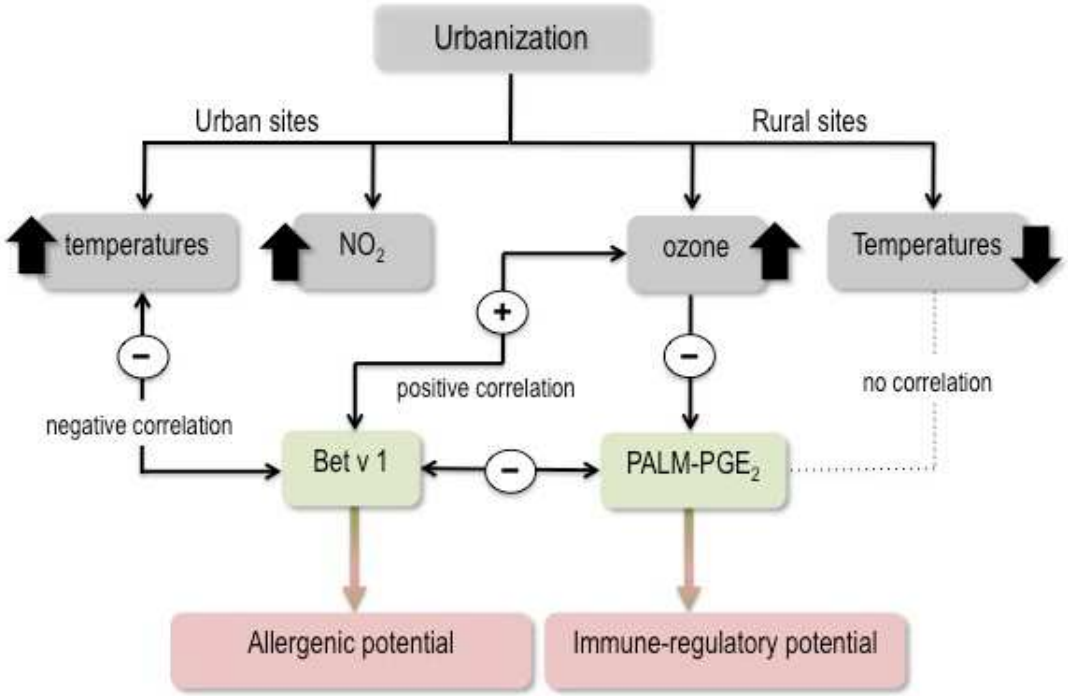

Figure 1 Modification induced by anthropogenic pollutants to pollen allergens.

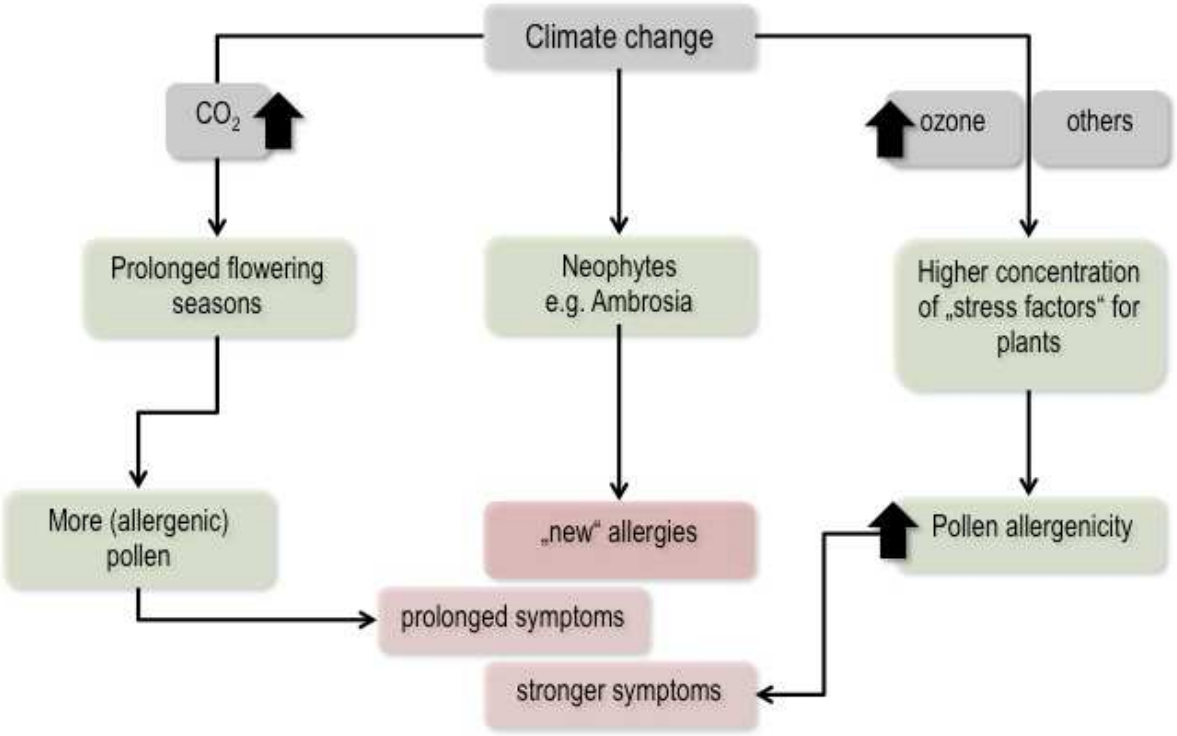

Figure 2 Climate change impact on the ecosystem of pollen-producing plants.

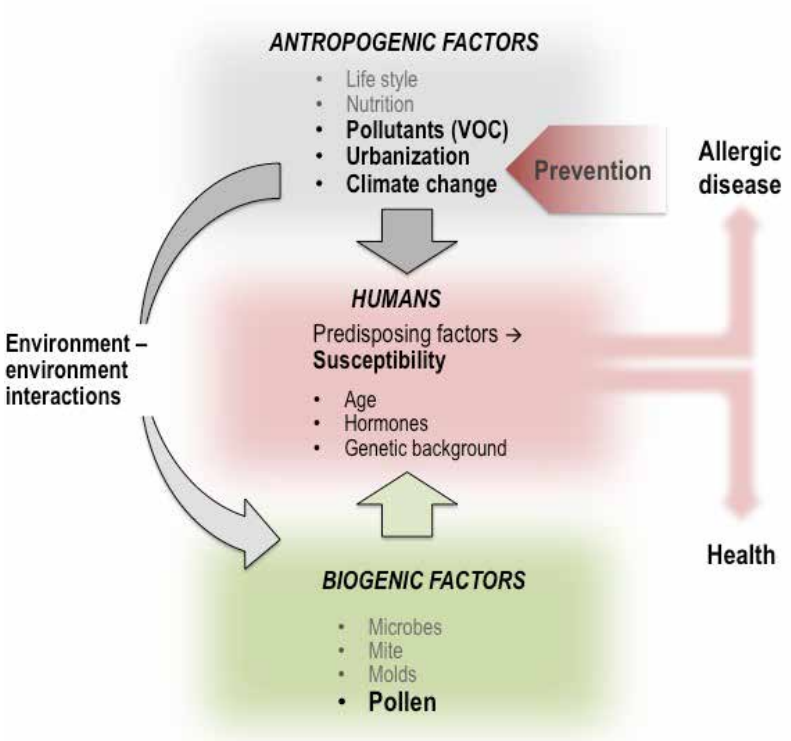

Figure 3 The complex interplay between host and environmental factors leading to allergic diseases: anthropogenic factors can act direct increasing susceptibility in genetic predisposed individuals or indirect by modifying/potentiating other biogenic factors.

lutants on humans, pollen-producing plants are themselves subject to modification by anthropogenic pollutants (Figures 1 and 2). We recently identified ambient ozone as a major factor influencing allergen content and adjuvant lipid composition of birch pollen. This illustrates how anthropogenic environmental factors, via their effect on the allergen carrier, can indirectly influence the health of allergic patients.

CLIMATE CHANGE RELATED RISKS

Global warming is associated with elevated CO2 levels and prolonged vegetation periods. This, in turn, causes prolonged flowering seasons, which might increase the load of allergenic pollen. The aggressive spreading of allergenic neophytes, such as *Ambrosia artemisiifolia*, in southeastern and parts of middle Europe already led to de novo sensitizations in the exposed populations. Moreover, exposure to Ambrosia pollen might induce symptoms even in mugwort-sensitized patients due to the high degree in inter-species cross-reactivity.

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4b MEASURING EXPOSURE TO ENVIRONMENTAL AIRBORNE ALLERGENS

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A key factor for the development of respiratory allergy is the contact between the respiratory organ and inhaled air containing the allergens. Airborne allergens can be found in a variety of sources (Table 1). The risks of respiratory allergy or elicitation of symptoms may be decreased by reducing exposure. Control measures should be based on allergen exposure monitoring performed according to well-defined and validated methods.

KEY MESSAGES

- Precise assessments of allergen concentrations is needed to define the exposure thresholds inducing sensitization, symptoms and exacerbations of allergic diseases
- The risks of respiratory allergy or elicitation of symptoms may be decreased by reducing exposure
- Control measures should be based on monitoring of allergen exposure performed according to well-defined and validated methods

To measure exposure to airborne allergens, it is imperative to report the presence of the sources of allergens (mite counts, presence of pets), because allergen levels can stay high when there are no sources or their number is low.

The choice of optimal procedures depends on the setting and objectives of allergen monitoring (Figure 1): epidemiological (population) studies on exposure-response relation, intervention studies, diagnosis and follow-up of individual patients, hazard identification for disease clusters, identification of cases of "new allergy", as part of routine monitoring or of a health surveillance program.

Indoor airborne allergen levels may be assessed in settled dust or in an air sample. A dust sample is collected from the bed, carpet or sofa by vacuuming a square yard area of the bed/carpet/sofa per 2 minutes with a vacuum cleaner with a collection device. The presence of allergens is quantified with an ELISA test. Recently, an alternative wipe sampling method has been implemented to collect allergens from floor dust, where allergens are measured by a real-time quantitative PCR methodology. However, methods using settled dust might not provide accurate measurements of inhaled allergens. To measure airborne allergens in the air, a technique has been developed that involves collecting an integrated total suspended particulate sample through an impactor. Extracts of air samples are then analyzed by a modified ELISA using an amplification of the generated colorimetric signal.

The prevalent outdoor allergens are pollens and molds. Usually, pollen and mold counts are assessed,and not their derived allergens.

A pollen count is nothing more than a measurement of how much pollen is in the air. It is expressed in terms of a concentration of pollen in the air in a specific area at a certain point in time. The exact measure is grains of pollen per cubic meter over a 24 hour period. Mold counts, like pollen counts, are a measurement of how many mold spores are in the air in a certain area at any given point in time. Monitoring pollen and mold counts on a daily basis during the

TABLE 1

Common airborne allergens and possible reaction(s)

Allergens		Where, when
Pollen *Lpl p 1, Phl p5, Cyn d1, Amb a 1, Bet v ...*		Outdoors Spring/summer/autumn
Mold *Alt 1, Cla 1 ...*		Both indoors (perennial) and outdoors (seasonal) . Indoors, molds can be found in any moist, dark place. Outdoors, mold results from vegetation degradation. Mold floats easily in the air.
House Dust mite (HDM) *Dermatophagoïdespteronyssinus (European HDM), Dermatophagoïdes farina (American HDM), Blomia tropiclais.* *Derp 1, Derf 1, Blo...*		Indoor Found in house dust, mattresses, bedding, upholstered furniture, carpets and curtains HDM feed on shedded flakes of skin HDM thrive in warm and humid environments.
Pets Cat (Feld1), Dog (Can1)		Indoor Major allergens are proteins secreted by oil glands in the animals' skin and shedded in dander as well as saliva proteins, which sticks to the fur when the animal licks itself. Urine is also a source of allergens. When the substance carrying the allergens dries they become airborne
Hamster, squirrel,rabbit	  	Indoor/occupational Urine is the major source of allergens from these animals.
Pests Mouse, rat, (Mus m1, Rat 1)	 	Urine is the major source of allergens from these animals.
Cockroach Blatella germanica (German cockroach) (Bla g 1)		Tiny protein particles shed or excreted by-cockroaches

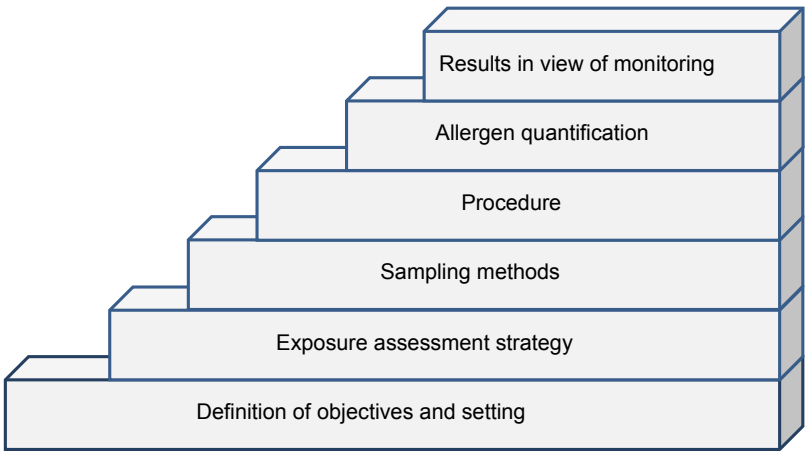

Figure 1 Stepwise selection process of methods and tools of allergen assessment (modified from ref. 1)

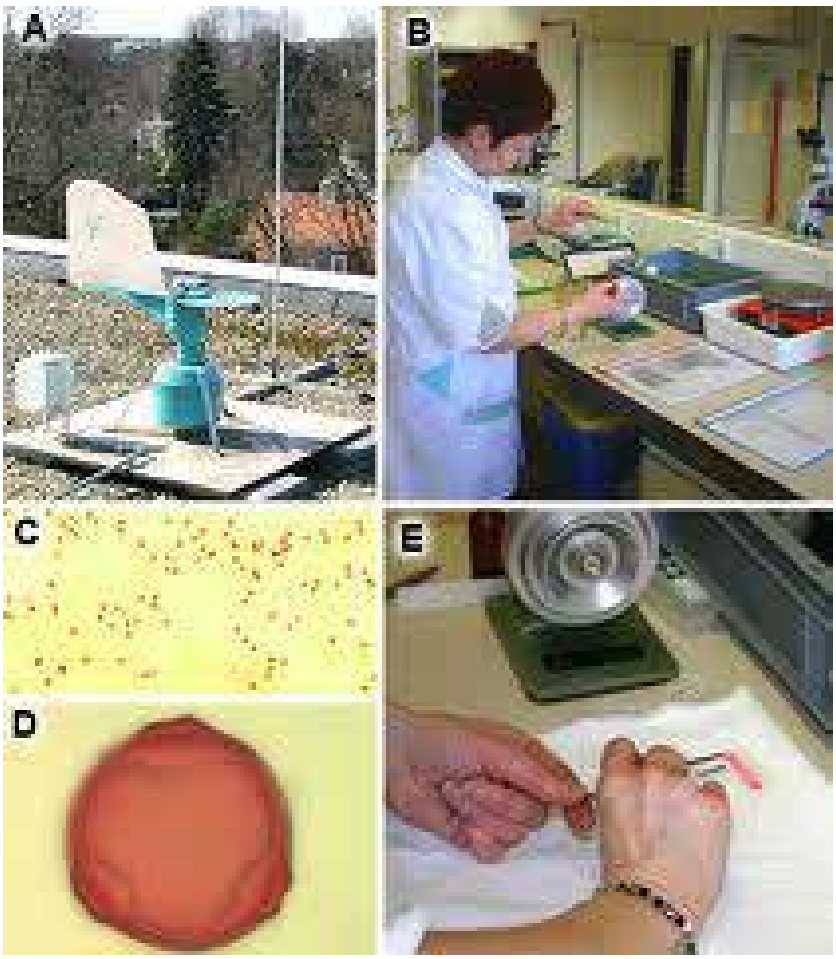

Figure 2 Pollen and mold assessment: A: pollen trap; B and E: ELISA measurement; C and D:microscopic evaluation of pollens and molds.

seasons when they are present is one of the most proactive steps to control asthma and allergies.Pollen and mold counts are collected using a special sampling trap that is typically placed on a rooftop several stories above the ground (Figure 2). The device has a sticky surface that collects grains of pollen and mold spore from the air. Specific pollen and mold are recognized using an electronic microscope.

Recent data have shown that pollen and mold counts do not represent allergen exposure. Air can be sampled for pollen and mold allergens with a high-volume cascade impac to requipped with stages for particulate matter (PM)>10 µm, 10 µm>PM>2.5 µm, and 2.5 µm>PM>0.12 µm. Allergenis determined with specific ELISA.

Precise assessment of allergen concentrations is needed to define the exposure thresholds inducing sensitization, symptoms and exacerbations of allergic diseases.

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4c

ENVIRONMENTAL RISK FACTORS FOR ALLERGY: FOOD

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KEY MESSAGES

- Environmental risk factors that may influence food allergy, together with atopy, include the "hygiene hypothesis", vitamin D insufficiency, reduced consumption of healthful dietary fats and antioxidants, and obesity
- Theories suggesting early infant ingestion of food allergens as a risk for allergy have been substantially disprove
- Early infant avoidance of food allergens could be a risk factor for allergy due to bypassing oral tolerance during a period of sensitizing cutaneous exposure
- Food allergy is the result of a complex interaction of genetic, immunologic and environmental influences, indicating a challenge for identifying effective prevention strategies

The prevalence of food allergy appears to have increased. Environmental factors must account for the apparent rise, not genetic predisposition. An over-arching effect may be the immune dysregulation attributable to the "hygiene hypothesis". Additional theories to explain increased atopy, with food allergy as a bystander, include vitamin D insufficiency attributable to greater use of sunscreens and less time outdoors, reduced consumption of healthful omega-3-polyunsaturated fatty acids and antioxidants, and increased obesity, which may represent an inflammatory state. However, for environmental influence on food allergy in particular, the role of exposure to food proteins becomes relevant.

Probably as a response to early studies suggesting that infants exposed to whole cow milk proteins were at higher risk of milk allergy compared to those receiving breast milk or hypoallergenic formula, among other observations, various expert panels and professional organizations suggested avoidance of allergens for infants at risk. Some guidelines included allergen avoidance during pregnancy and lactation. The goal was to prevent exposure to food allergens for a presumed immature and allergy-prone immune system.

However, mounting studies suggest that extended avoidance of food allergens may be a risk factor for food allergies, rather than preventative. Why would this be? One possibility is that earlier exposure allows for oral tolerance. For example, in a study of the rate of peanut allergy among Jewish children in the United Kingdom compared to Israel, there was a ten-fold higher rate of allergy in the UK, where early peanut consumption was comparatively very low (Figure 1). Timing of ingestion may only be part of the story. Non-ingestion routes of exposure may be strongly sensitizing: for example, despite ingestion of raw fruits, many persons develop pollen-food related syndrome caused by inhalation of food-homologous proteins in pollens, bypassing oral tolerance. Similarly, it was suggested that topical exposure, especially via inflamed skin, i.e., atopic dermatitis, during abstinence from oral exposure could be a sensitizing route bypassing oral tolerance (Figure 2). Additional evidence is the observation that household consumption rates of peanut, particularly messy products that increase environmental exposure, are a risk factor for peanut allergy, especial-

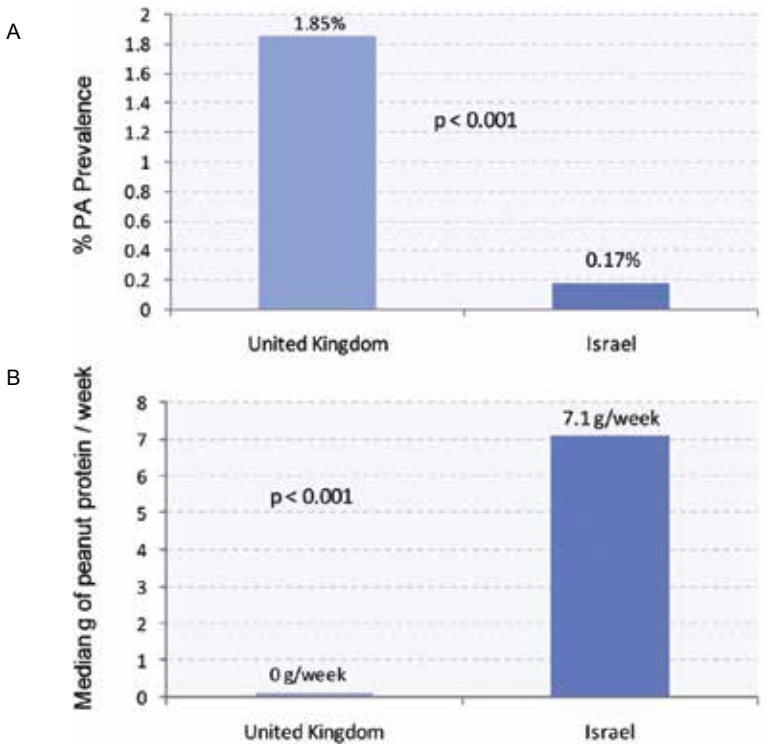

Figure 1 Earlier consumption of peanut was associated with a lower rate of peanut allergy. A - Prevalence of peanut allergy in children 4-18 years; B - Peanut protein consumption 8-14 month; United Kingdom n=5171; Israel n= 5615. (*Data from Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 2008; 122(5):984-91. Reprinted from J Allergy Clin Immunol, 129/5, Lack G. Update on risk factors for food allergy, 1187-1197, Copyright 2012, with permission from Elsevier.*)

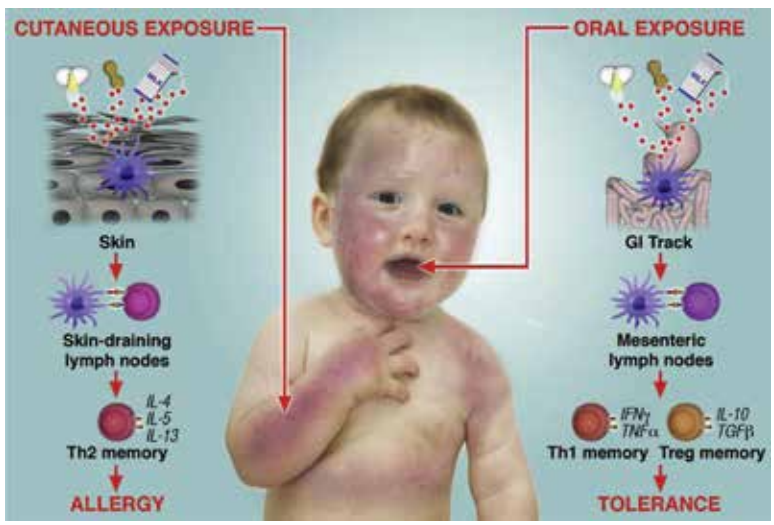

Figure 2 Cutaneous exposure to a food allergen, especially to inflamed skin, may be a sensitizing route. With a concomitant lack of oral exposure to induce tolerance, the effect could be promoting food allergy. (*Reprinted from J Allergy Clin Immunol, 129/5, Lack G. Update on risk factors for food allergy, 1187-1197, Copyright 2012, with permission from Elsevier.*)

ly if the infant has not ingested peanut early. Prior recommendations to avoid food allergens during pregnancy, breastfeeding and for children during weaning have been substantially rescinded, although counter-examples remain (Figure 3) and more studies are needed. Ultimately, the environmental and genetic determinants of food allergy are complex, presenting a challenge for identifying prevention strategies (Figure 4).

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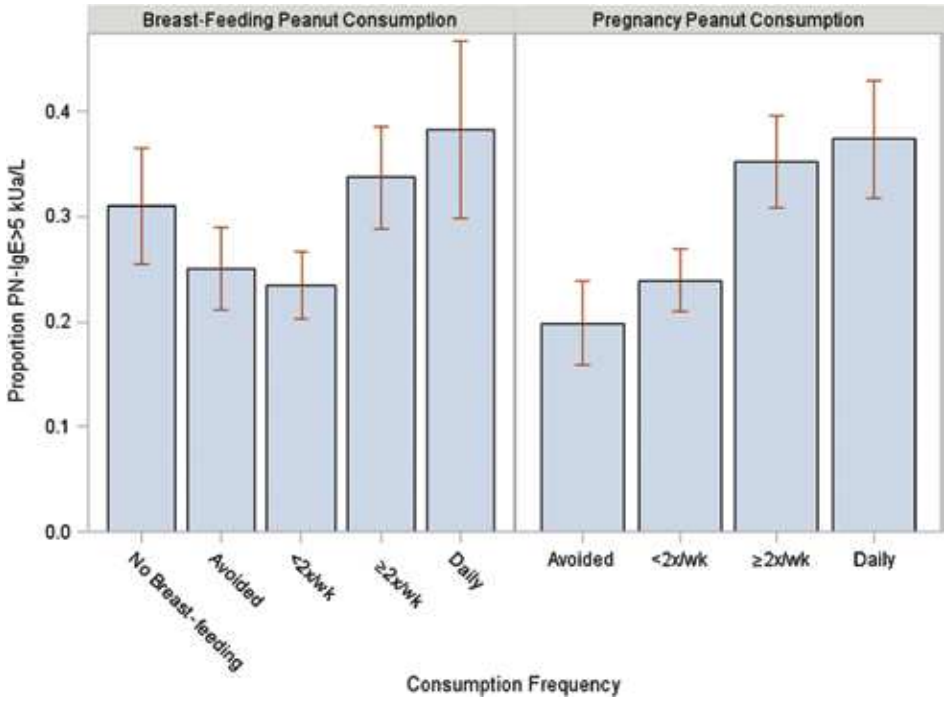

Figure 3 Although some studies suggest maternal ingestion of allergens during pregnancy or lactation does not increase the risk of sensitization/food allergy, there remains some controversy and more studies are needed. Here, a study of high risk infants suggests higher maternal ingestion of peanut during pregnancy is related to higher peanut IgE antibody levels in early infancy (P trend < 0.001). (*Reprinted from J Allergy Clin Immunol, 126/6, Sicherer SH, Wood RA, Stablein D, et al. Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants, 1191-1197, Copyright 2010, with permission from Elsevier.*)

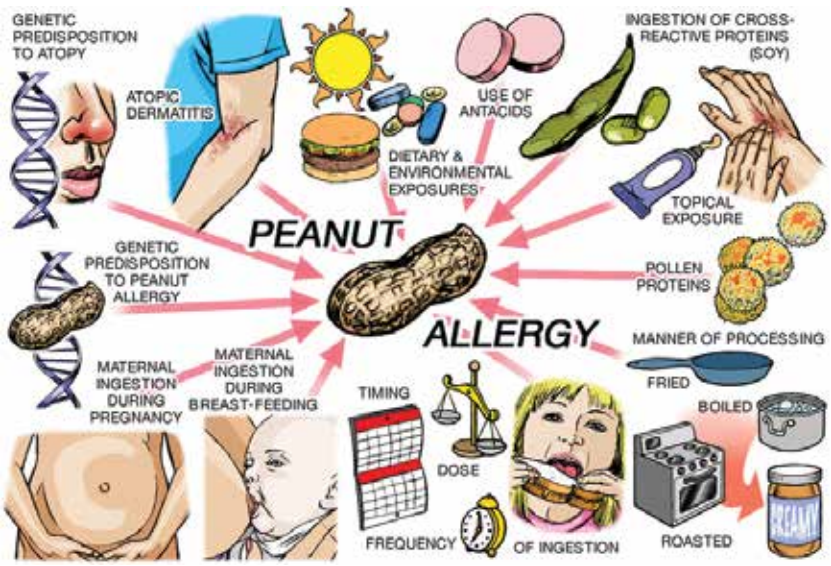

Figure 4 A complex interplay of genetic, immunologic and environmental influences likely conspires to result in food allergy, here with peanut as an example. (*Reprinted from J Allergy Clin Immunol, 120/3, Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic, 491-503, Copyright 2007, with permission from Elsevier.*)

4d ENVIRONMENTAL RISK FACTORS FOR ALLERGY: HOME ENVIRONMENT

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KEY MESSAGES

- During the last half of the 20th century, the perennial indoor allergens progressively increased in importance and became the primary allergens related asthma worldwide
- While the individual's home is an important site of exposure, it is now clear that exposure to indoor allergens in other homes or schools can play an important role in sensitization and in symptoms
- Comparing sensitization of children with asthma in different communities makes it clear that the community prevalence of a particular allergen may be as important as the specific levels in the child's home
- Although dust mites are ubiquitous in damp climates, they may be completely absent in ultra-dry environments such as Norbotten in Sweden and apartments in Chicago

THE RISE IN INDOOR LIVING AND THE RISE IN ASTHMA

The dramatic rise in electronic indoor entertainment from 1950 to 2000 paralleled the rise in asthma among children. The resulting changes in lifestyle led to both a major increase in time spent indoors and progressive "improvements" in homes. These changes not only allowed accumulation of allergens in fitted carpets, sofas, bedding, etc. but in humid climates allowed abundant growth of dust mites. Over this same period, almost all studies have shown strong associations between sensitization to indoor allergens and asthma in children over 5 years old and young adults (Table 1).

EXPOSURE IN THE HOME AND IN THE COMMUNITY AS A CAUSE OF SENSITIZATION

Children spend up to 95% of their time at home, at school or in other enclosed spaces. Initially it was assumed that the home had to be the primary site of sensitization; however, two findings have confused the simple message.

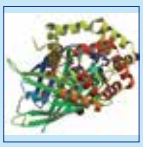
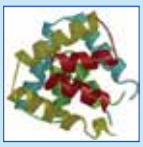
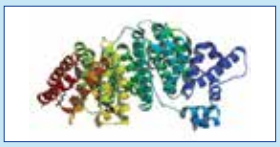
1. Studies designed to avoid exposure to dust mite carried out in Manchester and Sydney have not succeeded in preventing sensitization to this allergen. The explanation for that finding appears to be that relevant exposure to mite allergens can occur in other houses. In cities in the UK or coastal Australia most other houses in the community will contain mites. In Northern Sweden or Chicago, very few children become allergic to mites because the houses are too dry for mite growth.
2. Many but not all studies on cat exposure have found less sensitization to cats among children with higher exposure (Figure 1). For cat allergens, it is now clear that Fel d 1 on dander particles is present in schools and homes without a cat. Thus, exposure of children without a cat is sufficient to cause sensitization.

RELATIONSHIP OF SENSITIZATION TO ASTHMA

Although sensitization to indoor allergens is strongly associated with asthma this relationship is not simple. Sensitization as judged by skin prick tests is common in non-asthmatic children and also may be common in rural villages in Africa or Ecuador, where none of the children have allergic asthma. However, one of the striking fea-

TABLE 1

The allergens related to asthma

Source	Particles	Allergen	MW (kDa)	Structure
 Dust mite		Der p 1 Der p 2 Der p 10 Der p 11	25 16 33 102	 
 Cockroach	 Frass	Bla g 1 Bla g 2 Bla g 4 Bla g 5	47 39 21 23	
 Cat		Fel d 1 Fel d 2 Fel d 4 Cat IgA	10 69 10 200†	 
 Alternaria		Alt a 1 Alt a 2 Alt a 3	17 22 14	
 Grass		Lol p 1	17*	

The allergens related to asthma are predominantly in the molecular weight range 15 KD to 50 KD, and most of the major allergens are present as a significant proportion (>10%) of the extracts used for skin testing or in vitro assays (www.allergen.org) However, the sources of cat, mite, cockroach or mold allergens generally do not become airborne, and the allergens themselves are too large to be volatile because the saturated vapor pressure of molecules >10,000 MW approaches zero. Thus all relevant exposure is in the form of particles. The aerodynamic properties of the particles determine how long they remain airborne and their volume decides how much allergen they can carry (5).

*†Glycosylated with alpha-gal; *Glycosylated with MUXF3*

tures of asthma among children and adults in westernized or post hygiene societies is that titers of IgE antibodies to mite, cockroach, cat and Alternaria may be very high i.e. ≥30 IU/ml. We have seen highly significant association between the titer of IgE antibodies to mite or cat and the severity of asthma (Figure 2). Furthermore, studying children in Costa Rica, we found a strong association between the titer of IgE antibodies to mite and the impact of community acquired rhinovirus infection on wheezing (Figure 2).

CONCLUSIONS

The increase in asthma has been documented as "wheezing" in ISAAC, as use of inhalers, or as presentation with acute asthma either to ED or hospital. In each of these settings, evaluation of sensitization has shown a strong correlation between asthma and the perennial and predominantly indoor allergens. In rural settings in Africa, Ecuador, Nepal, etc., sensitization as judged by skin prick tests may be present, but wheezing is more likely to correlate with evidence of Ascaris or other parasitic infections. In recent studies, in Costa Rica, New Zealand, Ghana, Ecuador and Norbotten,

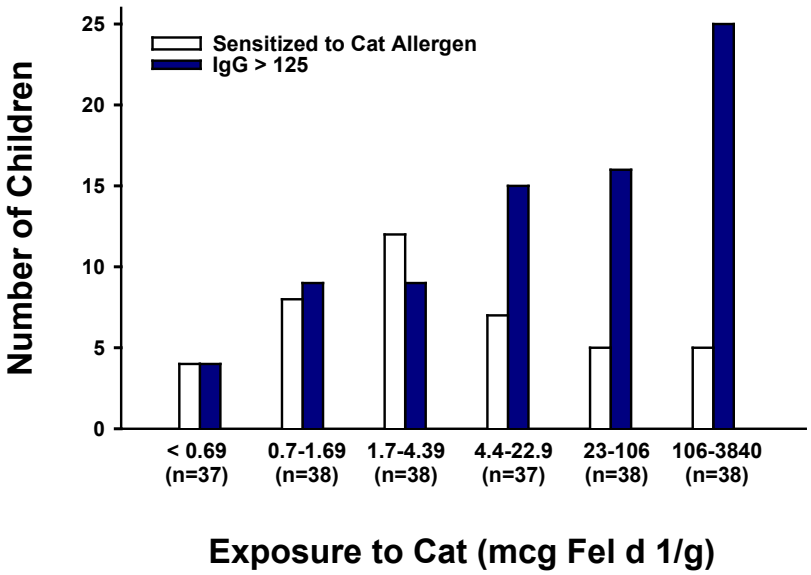


Figure 1 Prevalence of sensitization to cat allergens and of IgG antibodies to Fel d 1 for six groups of middle school children (age 11 years) with a wide range of concentrations of Fel d 1 in the dust from their homes. In the highest exposure groups, the prevalence of IgG to Fel d 1 was higher while the prevalence of sensitization was significantly lower. (*Reprinted from The Lancet, 357, Platts-Mills T,Vaughan J, Squillace S, et al. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study, 752-756, Copyright 2001, with permission from Elsevier.*)

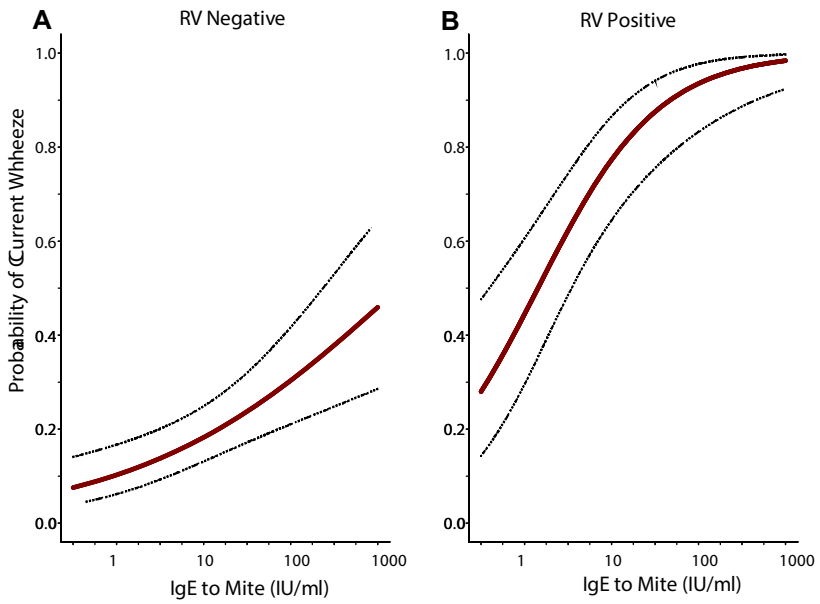


Figure 2 Probability of current wheeze based on increasing titers of IgE antibodies to D. pteronyssinus in children with negative tests for rhinovirus by using real time PCR (A) compared to children with positive test results for rhinovirus (B). (*Reprinted from J Allergy Clin Immunol, 129/6, Soto-Quiros M, Avila L, Platts-Mills TA, et al, High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus., 1499-1505, Copyright 2012, with permission from Elsevier.*)

there is consistent evidence that the western model of asthma relates to higher titers of IgE antibodies to one or more of the perennial allergens. Thus, overall we have a model where, increased time spent indoors in overheated and under ventilated buildings leads to sensitization to the predominant allergen in the community, which may be derived from mites, cockroaches, or animal dander. The major rise in prevalence of asthma in children is most likely to be due to the combination of increased exposure to indoor allergen and the associated sedentary lifestyle.

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4e ENVIRONMENTAL RISK FACTORS FOR ALLERGY: WORKING ENVIRONMENT

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KEY MESSAGES

- Sensitizers (high and low molecular weight allergens, HMW, LMW) and irritants may lead to work-related respiratory disease. There is overlap between the different categories of eliciting agents. Sensitizers may also have irritating properties. Irritants may lead to new onset occupational disease, but also to worsening of pre-existing disease
- The level of exposure is considered as the key factor for the development of occupational rhinitis and asthma
- Atopy is a risk factor for the development of IgE-mediated sensitization to HMW allergens. However, the presence of atopy cannot be used to identify and exclude susceptible workers
- The influence of smoking on development of occupational allergy may dependent on the specific allergens involved

Environmental agents at the work place may lead to several allergic and non-allergic conditions. Occupational rhinitis or asthma, but also occupational chronic cough may develop upon exposure to agents at work. Sensitizing agents - in most cases high molecular weight (HMW) allergens, and sometimes low molecular weight (LMW) allergens – may induce an IgE mediated allergic reaction, responsible for allergic occupational rhinitis and asthma. Less frequently, single or multiple exposures to irritants will lead to non-allergic irritant-induced occupational rhinitis or asthma. Apart from these occupational diseases caused by work, environmental stimuli at work may also lead to worsening of pre-existent rhinitis, asthma or cough (work exacerbated rhinitis, asthma or cough). Figure 1 shows examples of allergens and stimuli responsible for the different work-related disorders. Chronic cough at work can be considered as a separate work-related disorder. Table 1 shows the occupations and causes of work-related chronic cough. There is some overlap between the different categories of eliciting agents. Sensitizers may also have irritating properties. Irritants may lead to occupational disease, but also to worsening of pre-existing disease.

The level of exposure is considered as the key factor for the development of occupational disorders. The risk increases with high exposure. Less is known of the impact of exposure pattern (duration, continuous or intermittent, peak exposures).

Apart from exposure, host factors may determine the risk of occupational rhinitis and asthma. Atopy is a risk factor for the development of IgE-mediated sensitization to HMW allergens in the working environment, and to a lesser extent for development of occupational rhinitis or asthma. The presence of atopy, however cannot be used to identify and exclude susceptible workers. Smoking has been associated with some work-related allergies such as allergies to bell peppers and platinum salts, but not in others. Possibly, the influence of smoking on development of occupational allergy dependents on the specific allergens involved. Finally, genetic factors may be associated with increased susceptibility to occupational asthma.

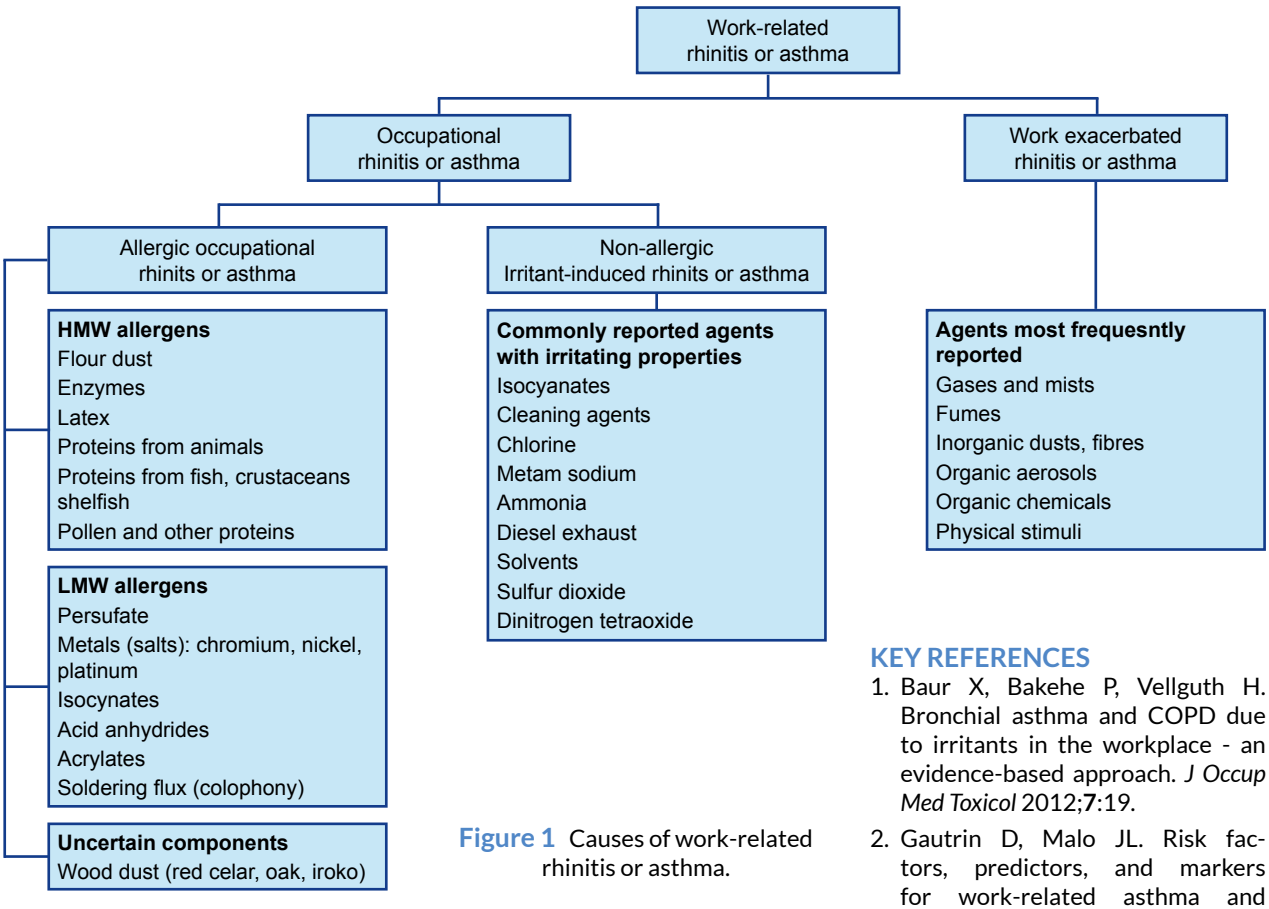

Figure 1 Causes of work-related rhinitis or asthma.

TABLE 1

Causal agents of work related chronic cough	
Occupation	**Agents**
Miners	Methylmethacrylate
Cement and glass bottle production	Aliphatic polyamines
Construction workers	Grain and flour mills
Farming workers	Spices
Food industry	Dust due to World Trade Center collapse
Mushroom factory	
Wood industry	Vapor Gases Dusts Fumes
Dental technicians	Cattle and swine confinement farms
Fire-fighters	Cleaning products
Bakery	Second-hand smoking
Mechanic and repair jobs	
Spice factory	
Greenhouse	
Cleaners	

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4f RISK FACTORS FOR CHILDHOOD ASTHMA: VIRAL INFECTION AND ALLERGIC SENSITIZATION

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KEY MESSAGES

- Preschool viral wheezing illnesses are risk factor for the development of childhood asthma, with human rhinovirus (HRV) having the greatest impact
- Aeroallergen sensitization in the first two to three years of life further increases the risk of developing asthma in children, who have viral-induced wheezing
- Rhinovirus wheezing illnesses may lead to asthma development through two pathways, dependent and independent on allergic sensitization

Asthma is the most prevalent chronic disease of childhood. Given its significant health as well as socioeconomic burden, investigators around the world have sought to define environmental and genetic factors that contribute to asthma inception in early life. One important environmental factor demonstrable in multiple studies has been respiratory tract infections. From a genetics perspective, atopy and genetic variation at the 17q21 locus (that appears to be independent of atopy), are risk factors for asthma development. Interestingly, both appear to be dependent, at least in part, on antecedent preschool human rhinovirus (HRV) wheezing illnesses.

EARLY CHILDHOOD RESPIRATORY VIRAL INFECTION AND ASTHMA IN CHILDHOOD

Although early childhood respiratory syncytial viral (RSV) infections have been documented to contribute to future asthma risk, recent advances in molecular diagnostic testing have enabled investigators to establish a relationship between HRV wheezing illnesses and asthma. In an evaluation of a high risk birth cohort, Jackson et al. found that infection with HRV in the first three years of life was the virus most significantly associated with the development of asthma at age 6 years (Figure 1).

Mechanisms responsible for these developments are currently being intensely evaluated. Wark et al. found that cells from asthmatic patients had decreased production of both type I and III interferons, two important cytokines in the host's innate immune response to viral infections. Recently, Caliskan and colleagues demonstrated that allelic variation at a highly replicable genetic locus for asthma was associated with significant asthma risk only in children who wheezed with HRV (not RSV) infections in early life. Since genes contained within this locus have functions that involve calcium membrane flux and the unfolded protein response, it is possible that alterations in these pathways may further influence host immune response to viral infections at critical times in the lung development. Recently, infections with HRV-C have been noted to be associated with more significant clinical illnesses that may be of even greater severity in atopic children.

COMBINED VIRAL INFECTION AND AEROALLERGEN SENSITIZATION

The relationship of atopy with the subsequent development of asthma is widely recognized. Aeroallergen sensitization in the first 2 to 3 years of life has been reported to be a risk factor for the subsequent development of asthma.

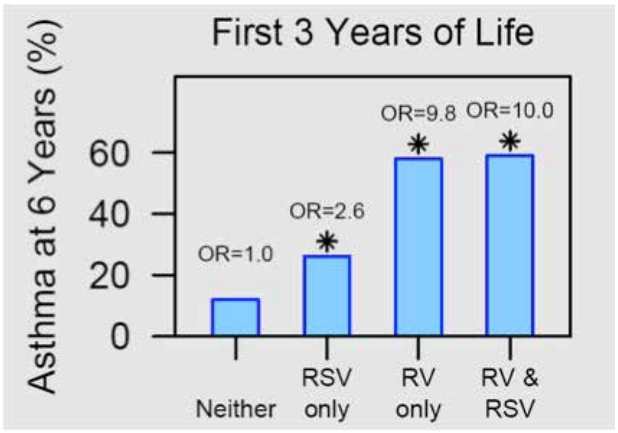

Figure 1 In an a high risk birth cohort infection with HRV in the first three years of life was the virus most significantly associated with the development of asthma at age 6 years.

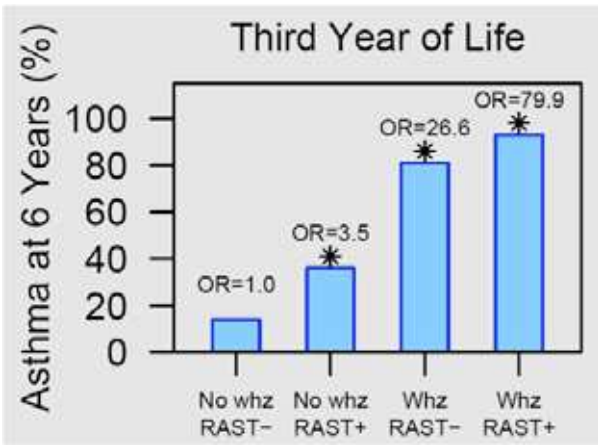

Figure 2 Aeroallergen sensitization without documented preschool RV wheezing increases asthma risk by age six years. If both RV wheezing and aeroallergen sensitization are present at age three, the risk of developing asthma by age 6 years is substantially increased.

The development of multiple early sensitizations increases not only the risk of developing childhood asthma, but its clinical severity in terms of hospital admission rates as well.

Preschool viral wheezing illnesses and the development of allergic sensitization can both independently increase asthma risk. The presence of both can further influence the development of asthma, as demonstrated by data generated independently in two high-risk birth cohorts. In one of the high-risk birth cohort, aeroallergen sensitization without documented preschool RV wheezing increased asthma risk by age six years (OR = 3.4) (Figure 2). If both RV wheezing and aeroallergen sensitization were present at age three, the risk of developing asthma by age 6 years was substantially increased (OR = 80).

Jackson et al. longitudinally evaluated which development occurs first: allergic sensitization predisposing to viral-induced wheezing, or the reverse. Using a four stage statistical model, the study found that allergic sensitization is more likely to precede viral-induced wheezing. Moreover, HRV wheezing illnesses were the most likely infections accounting for this temporal developmental sequence. Allergic sensitization may increase lower airways inflammation and symptoms based on the ability of IgE receptor numbers and bridging to be associated with reduced dendritic cell production of type I and type III interferons with decreased viral host defense (Figure 3).

INFLUENCE OF HRV WHEEZING ILLNESSES INDEPENDENT OF ATOPY

Genome-wide association studies of childhood asthma risk have revealed a high susceptibility locus on chromosome 17q21. Genetic variation in this 17q21 region has been associated with increased childhood asthma risk but not with atopy. Caliskan and colleagues demonstrated that this association is in fact limited only to children who had HRV wheezing illnesses in the first three years of life.3 Importantly, this genotype-attributable increased risk is totally independent of allergic sensitization (atopy).

CONCLUSION

At least two distinct mechanistic pathways may predispose children to asthma (Figure 4), both dependent on antecedent HRV wheezing illnesses. The first pathway, termed 17q21, appears to be dependent on an asthma susceptibility locus and totally independent of the presence of allergic sensitization. The second pathway, termed FcεRI, is dependent on the development of allergic sensitization. Continued evaluation of mechanisms responsible for these pathways hopefully will provide insight into disease treatment and prevention strategies.

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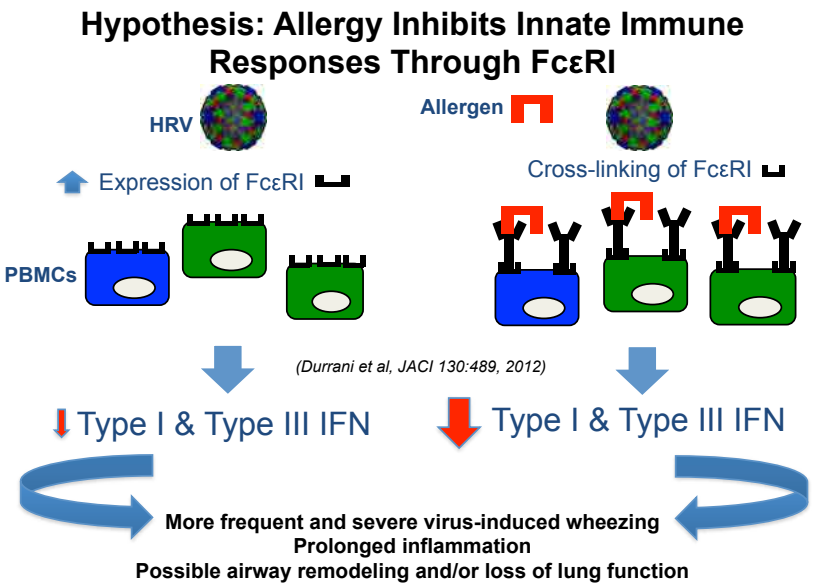

Figure 3 The process of allergic sensitization may influence innate immune responses to human rhinovirus (HRV) infection. Incubation of peripheral blood mononuclear cells (PBMCs) with HRV without cross linking of the high affinity receptor for IgE antibody (FcεRI) (left panel) results in decreased production of type I and type III interferons (IFN). Following cross-linking of this receptor (right panel) this decrease is further reduced.

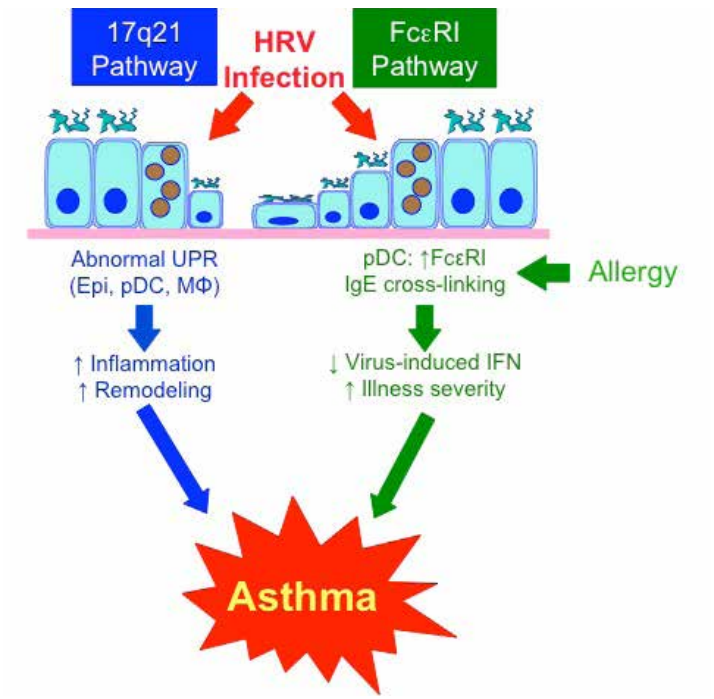

Figure 4 Two distinct mechanistic pathways dependent on antecedent HRV wheezing illnesses predispose children to asthma. The first pathway, termed 17q21, appears to be dependent on an asthma susceptibility locus and totally independent of the presence of allergic sensitization. The second pathway, termed FcεRI, is dependent on the development of allergic sensitization.

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4g ENVIRONMENTAL RISK FACTORS FOR ALLERGY: HELMINTH INFECTIONS

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KEY MESSAGES

- In developing countries, large differences exist in the prevalence of allergies between rural and urban areas as well as between high and low socioeconomic status (SES) groups within urban areas
- Helminth infections, which are ubiquitous in rural areas and among low-SES urban dwellers, drive T-helper 2 (Th2) responses
- High levels of total IgE and allergen-specific IgE are seen in helminth-infected subjects, but these do not translate into skin reactivity or clinical symptoms
- Regulatory network induced by helminths and helminth-induced IgE cross-reactivity prevent the translation of Th2 responses into allergic disorders
- Allergen-specific IgE has limited diagnostic value for allergic disease in helminth-endemic areas

Over 1 billion people worldwide are infected with parasitic worms. Most of these individuals are found in tropical regions of the world, where such infections are linked to poverty and rural living. Both helminths and allergens are potent inducers of T helper 2 (Th2) responses that lead to high levels of immunoglobulin (Ig) E, tissue eosinophilia, mast cells as well as the secretion of Th2 cytokines such as interleukin (IL)-4, IL-5, IL-9 and IL-13.

Despite the similar immunological profiles associated with both helminths and allergies, there is little overlap in the geographical distribution of these two health problems. Moreover, in developing countries, among urban populations of high socioeconomic status (SES), improved hygiene and fewer infections have been linked to an increase in allergic disorders. Indeed, a number of studies have found a negative association between helminth infections and allergic disorders among rural and low SES urban populations within these countries (Figure 1).

Mechanistically, chronic helminth infections have been shown to induce an immune regulatory network in the host characterized by regulatory T and B cells, alternatively activated macrophages and modified dendritic cells (Figure 2). This leads to an anti-inflammatory environment that prevents the down-stream effector phase of Th2 responses associated with allergic disorders. However, the timing and duration of helminth infection are key, since infections early in life and/or chronic infections are more effective in down-modulating allergic disease. In addition, the species of helminth is also an important determinant in the modulation of allergic disorders.

Another mechanism that might explain the inverse association between helminth infection and allergy may involve helminth-induced IgE cross-reactivity. Current helminth infections are associated with increased levels of allergen-specific IgE that do not translate into skin reactivity or clinical symptoms (Figure 3). Moreover, this helminth-induced IgE appears to be of low affinity and does not lead to mast cell degranulation.

In fact, in developing countries, strong correlations are observed between allergen-specific IgE and symptoms of allergy among urban

Figure 1 Allergy field research in a helminth-endemic area on Flores Island, Indonesia. The study showed an inverse association between current helminth infection and skin prick test positivity to house dust mite in a semi-urban population. (From Hamid F, Wiria AE, Wammes LJ, Kaisar MM, Djuardi Y, Versteeg SA, Wahyuni S, van Ree R, Sartono E, Supali T, Yazdanbakhsh M. Risk Factors Associated with the Development of Atopic Sensitization in Indonesia. PLoS One. 2013 19;8(6) :e67064).

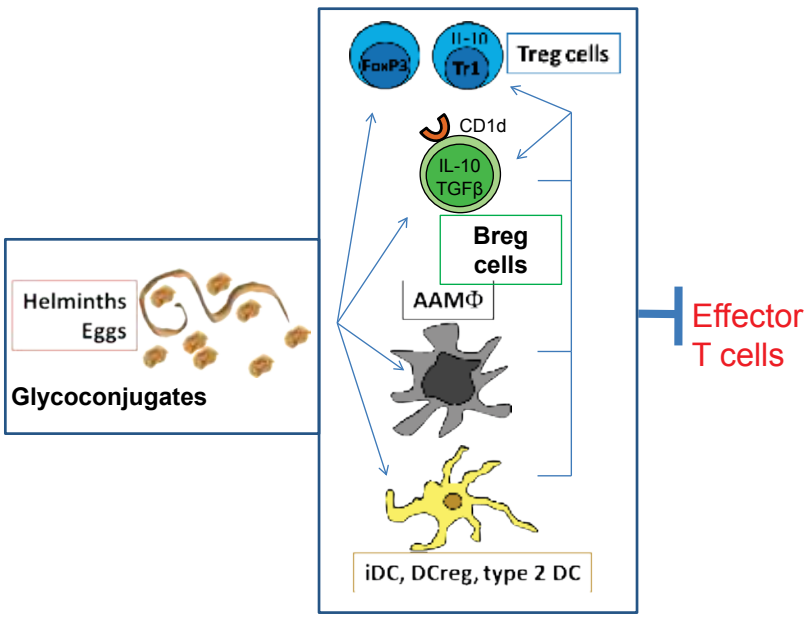

Figure 2 Helminths and their products induce an immune regulatory network in the host characterized by regulatory T (Tregs), regulatory B cells (Bregs), alternatively activated macrophages (AAMΦ) and modified dendritic cells (immature dendritic cells [iDC] and regulatory dendritic cells [DCreg]).

populations of high SES. However, in rural populations as well as urban low SES groups, helminth-induced IgE cross-reactivity and regulatory networks may prevent the translation of allergen-specific IgE into skin reactivity or allergic symptoms (Figure 4). Therefore, allergen-specific IgE has limited diagnostic value for allergic disease in helminth-endemic areas.

Future studies taking an international perspective will be essential for our understanding of environmental risk factors and underlying mechanisms to develop new treatments that can halt the allergy epidemic worldwide.

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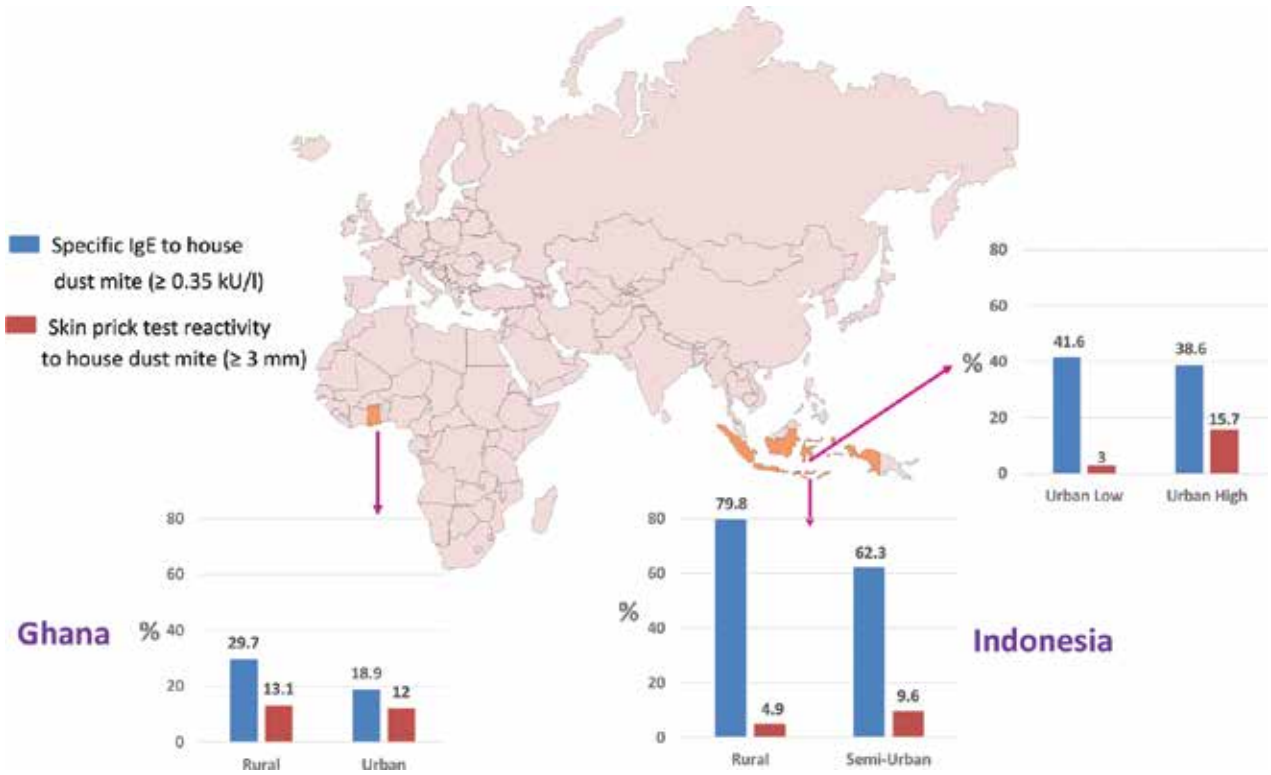

Figure 3 Differences in the prevalence of mite sensitization when measured as IgE or as SPT among 5-16 year olds from three populations living in Ghana (urban and more rural areas of the Greater Accra region which is undergoing rapid urbanization) and on two Islands in Indonesia (semi-urban and rural parts of Flores Island as well as among high SES and low SES subjects living in an urban centre of Sulawesi Island). The data presented are from Hamid F, Wiria AE, Wammes LJ, Kaisar MM, Djuardi Y, Versteeg SA, Wahyuni S,van Ree R, Sartono E, Supali T, Yazdanbakhsh M. Risk Factors Associated with the Development of Atopic Sensitization in Indonesia. PLoS One. 2013 19;8(6) :e67064 as well as unpublished data from field studies in Ghana and Sulawesi, Indonesia.

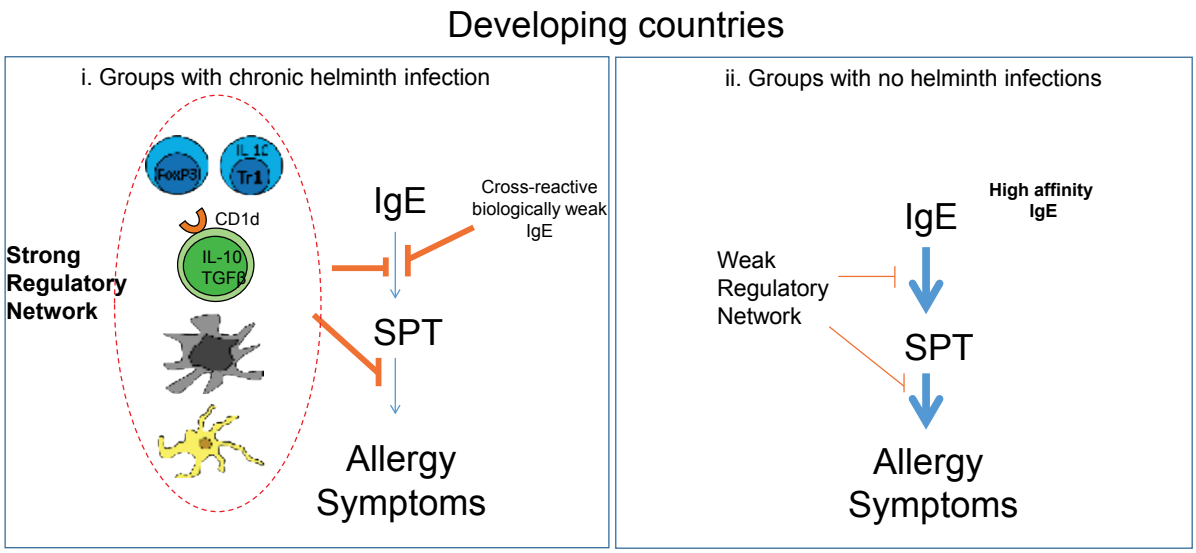

Figure 4 (i) In developing countries, the regulatory network induced by helminths and helminth-induced IgE cross-reactivity prevent the translation of Th2 responses into allergic disorders among groups with chronic helminth infections. (ii) In the same countries, among groups with no helminth infections, specific IgE translates into skin prick test positivity and allergy symptoms from field studies in Ghana and Sulawesi, Indonesia).

5 PERINATAL IMMUNE DEVELOPMENT AND ITS ROLE IN ATOPY DEVELOPMENT

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KEY MESSAGES

- programming of long-term sensitization versus tolerance to allergens occurs in early life against a background of functional immaturity within the immune system
- slow postnatal maturation of immune functions increases sensitization risk
- multiple cell types within the innate and adaptive immune system exhibit slow maturation kinetics in children, who subsequently develop atopy
- postnatal maturation is driven by microbial signals, particularly from gut commensals
- the trajectory for postnatal immune development is partially present *in utero*, driven via signals present in the maternal environment, including microbial exposures

Interest in the role of immune development as a risk factor for atopy was first stimulated by experimental studies on the sequelae of *de novo* exposure of immunologically naïve animals to aeroallergen. Such exposure triggered an initial "default" response comprising low-level Th2-immunity, including specific IgE production, which was eventually terminated by emergence of specific T-regulatory cells (Tregs) that induced a state of long-lived immunological tolerance, protecting the animals against sensitization at subsequent re-exposures. These findings served to focus human studies on the etiology of atopy on the life period (infancy), during which the naïve immune system first encounters allergens. A number of resultant observations attest to the validity of this approach:

(i) data from birth cohorts (Fig 1) demonstrate an initial induction of aeroallergen-specific IgE in both atopic and non atopic children during infancy, preceding subsequent stabilization of "tolerized" versus "sensitized" immunophenotypes, as the immune system progressively programs alternate forms of T-cell memory;

(ii) the rate of postnatal maturation of Th-cell functional competence (as measured by capacity to generate "balanced" Th1/Th2 cytokine responses) is slower in children at high risk for allergy development;

(iii) subsequent studies have extended the range of cell types manifesting atopic risk-associated developmental deficiencies to additional populations within the innate and adaptive immune system including monocytes, dendritic cells and Tregs.

Following the advent of the Hygiene Hypothesis in the late 1980s, interest has progressively increased in the role of the gut microbiome as the "driver" of postnatal development of immunocompetence. Recent findings suggest a link between postnatal development of immunity to organisms within the respiratory microbiome and risk for atopic asthma.

Since many of these functional deficiencies are already evident in cord blood the trajectory for postnatal immune maturation seems at least partially preset before birth. Observations stemming from the "farm barn" studies in Europe

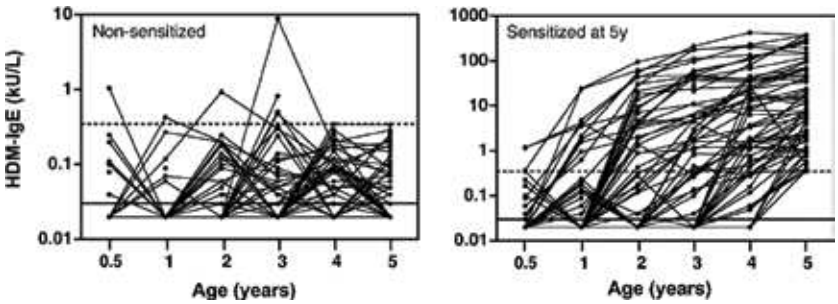

Figure 1 Postnatal development of sensitization versus tolerance to house dust mite (HDM). Fluctuations in HDM-specific IgE titers in individual children who were not (left) or were (right) sensitized at age 5 years. The dotted line indicates the 0.35 kU/L sensitization threshold. Note "cycling" of IgE production, particularly in non atopics, reflecting underlying competitive interactions between regulatory and helper T-cell populations. (© *Holt et al 2010 originally published in J Allergy Clin Immunol 125(3), 645-651. Reprinted under Rightslink Lic No 3346780104940.*)

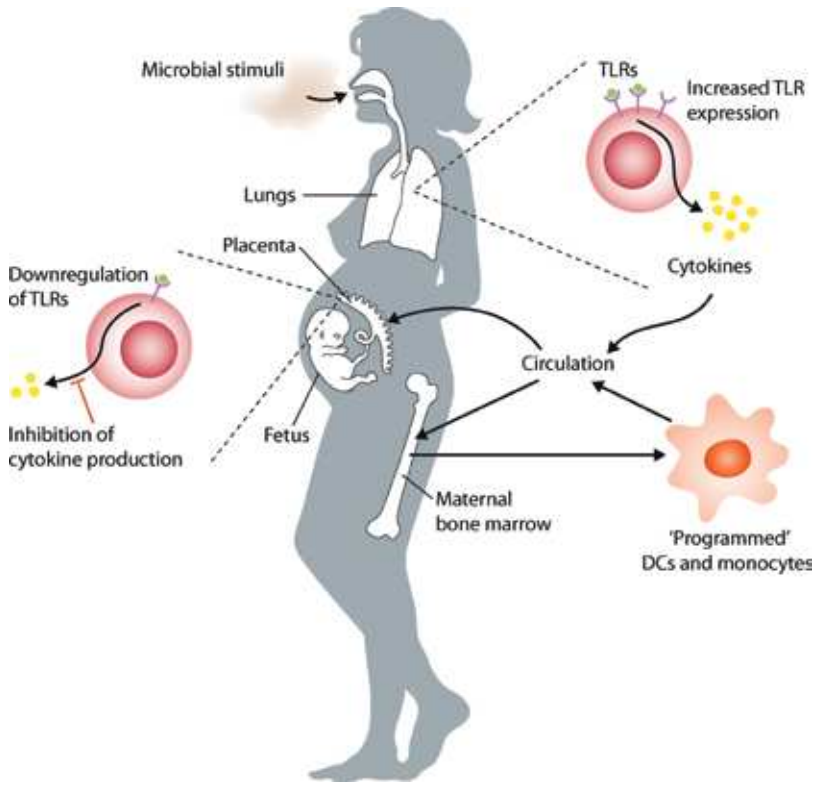

Figure 2 Proposed mechanisms by which maternal exposure to bacteria protects against allergies in offspring. A multi-step process may be involved: (i) initial mild-to-moderate inflammation in the lungs induced by aerosol exposure to microbe-containing dust; (ii) resultant cytokine signals translocate from lung to placenta via the bloodstream, where they attenuate local TLR expression and modulate resident myeloid cell functions; (iii) circulating cytokines enter the maternal bone marrow, where they "program" myeloid precursors that subsequently traffic to the decidua to replenish resident myeloid populations and influence the local inflammatory milieu. (*Reproduced with permission from Patrick G. Holt, et al. Soothing signals: transplacental transmission of resistance to asthma and allergy. J Exp Med. 2009;206(13):2861-2864.*)

have identified TLR-dependent microbial signaling to innate immune cells in the maternal decidua as the potential mechanism: this may result in stabilization of the immunological milieu in the placenta, contributing to protection of the integrity of the local vasculature responsible for delivering nutrients to the fetus, thus optimizing *in utero* growth and development (Figure 2).

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6 PERINATAL RISK AND PROTECTIVE FACTORS FOR ALLERGIC DISEASES

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KEY MESSAGES

- The development and phenotypic expression of allergic disease depends on a complex interaction between genetic factors, environmental factors (food or inhalant allergen exposure) and risk/protective factors
- The concept of the *hygiene hypothesis* has been extensively investigated and has influenced our understanding of early-life events
- Some susceptible/predisposed individuals may benefit from reduction of allergen exposure
- Exposure to food or inhalant allergens cannot be totally avoided, and observational and interventional studies on avoidance/reduction of exposure have not shown convincing results
- Multifaceted allergy avoidance during infancy with avoidance of both foods and airborne indoor allergens have shown a persisting reduction of asthma

The development and phenotypic expression of allergic disease depends on the interaction between genetic and environmental factors such as exposure to allergens together with risk and/or protective factors (Table 1). Over the last decades an increase in the prevalence of allergic diseases has been reported worldwide. From prospective birth cohort studies, possible protective and risk factors have been identified (Table 2, 3). A family history of allergic disease (asthma, allergic rhinoconjunctivitis, atopic eczema or food allergy) in first degree relatives, is strongly associated with an increased risk for allergic disease.

Considering that the increase in the prevalence of allergic diseases cannot be ascribed solely to genetic factors, most studies on development of allergic diseases have focused on the influence of in environmental factors, e.g. early feeding (breastfeeding vs. cow's milk formula), diets/nutrients, exposure to allergens, tobacco smoking, pollution, farm vs. urban environment, and infectious load. Many hypotheses have been proposed based on observed associations between environmental factors and development of allergic diseases. Such associations can only be used for generation of hypotheses.

Many hypotheses on causes of the increase in allergic diseases have been suggested, most often without convincing and consistent results (Table 4). The concept of the *hygiene hypothesis* has been extensively investigated and has influenced our understanding of early-life events. According to this hypothesis, early exposure to common bacterial triggers such as endotoxins, LPS or helminths might have an allergy preventive effect. The hygiene hypothesis may in part explain the increase in the incidence of allergic diseases . However, multifactorial environmental factors may play a role and interact (Table 3).

A strong association between *exposure to allergens* and IgE sensitization has been documented and also a strong association between sensitization and development of allergic disease, such as allergic asthma and rhinoconjunctivitis. Sensitization to foods appears first, followed by sensitisation to indoor allergens (e.g. house dust

TABLE 1

Development of allergic disease

The development and phenotypic expression of allergic disease depends on a complex interaction between:
• Genetic factors
• Environmental factors
  ▪ food allergen exposure
  ▪ inhalant allergen exposure
• Risk/protective factors e.g.
  ▪ tobacco smoke
  ▪ microbials, endotoxins, LPS
  ▪ infections
  ▪ diet (nutrients/foods)
  ▪ other

Age, dose and duration of exposure are important **Synergistic effects**

TABLE 2

Predictors for sensitisation and persistent allergic disease
Predictors for sensitization and allergic disease
• Atopic heredity
• Elevated cord blood IgE
• Early sensitization to foods and aeroallergens
• Persistent sensitization
Predictors for persistent allergic airway disease into adolescence/adulthood
• Persistent sensitization
• High degree sensitization and polysensitization
• Early onset of persistent asthma
• Severe disease
• Reduced lung function
• Presence of another atopic disease

TABLE 3

Possible environmental factors influencing development of allergic diseases	
Risk factors	**Protective factors**
Allergen exposure	Exclusive breastfeeding 4-6 months
Tobacco smoke?	Early exposure to endotoxins, LPS, helminths?
Lack of breastfeeding?	Infections?
Early introduction of solid foods?	Diets/nutrients? Antioxidants, lipids, probiotics, vitamins
Mode of delivery (Caesarean section)	
Infections?	
Early treatment with antibiotics?	

TABLE 4

Hypotheses on causes of increase in allergic diseases
• Changes in dietary factors
• Changes in allergen exposure
• Modified infectious load – hygiene hypothesis
• Pollutants/irritants
• Obesity
• Life style factors

mites, pets) and later by sensitisation to outdoor allergens (e.g. pollen, mould). However, sensitization may be a transient normal phenomena followed by development of tolerance.

THE CONCEPT OF AVOIDANCE

For decades, primary prevention addressing prevention of sensitization and development of clinical allergic disease has mostly focused on avoidance of exposure to allergens (e.g. foods, indoor allergens). Over the last decade, a new concept of primary prevention has emerged. Earlier it was believed that breastfeeding and avoidance of cow's milk proteins could prevent development of cow's milk protein allergy. However, human milk contains cow's milk proteins, if the mother has an intake of cow's milk. Other food proteins are also present in human milk. Thus, foreign proteins cannot be avoided by exclusive breastfeeding. The concept of avoidance of foods during breastfeeding is wrong. Infants are exposed to small amounts of foreign proteins (*reduced exposure*), which may rather lead to tolerance than to clinical allergic disease. Furthermore, breast milk contains many immune-modulating factors that may influence the development of allergy (Table 5).

TABLE 5

Factors in human milk influencing development of allergy

Factors	Inducing	Protective
Antigens (e.g. food proteins)	Sensitising allergens	Tolerising allergens
Cytokines	IL-4	TGF-beta
	IL-5	sCD 14
	IL-13	
Immunoglobulins		s-IgA
PUFA	Arachidonic acid	N3-PUFA
	N-6 PUFA	Other

TABLE 6

Evidence-based recommendations for primary prevention of food allergy

For all infants:

- No special diet during pregnancy or for the lactating mother
- Exclusively breastfeeding for 4-6 months

Further recommendations for infants with atopic predisposition:

- If supplement is needed during the first 4 months a documented hypoallergenic formula is recommended

Introduction of complementary foods after the age 4 months according to normal standard weaning practices and nutrition recommendations for all children irrespective of atopic heredity

TABLE 7

Evidence-based recommendations for prevention of allergy to inhalant allergens

- Avoid exposure to tobacco smoke
- Avoid pets at home if parents or siblings are allergic to pets

Common sense:

- Restrict exposure to house dust mites and pets for children with atopic disposition

Other routes of exposure occur via inhalation (proteins in house dust), or via the skin. Likewise, exposure to inhalant allergens cannot be totally avoided, and observational and interventional studies on avoidance/reduction of indoor allergen exposure (house dust mite, cat) have not shown convincing results. However, multifaceted allergy avoidance during infancy with avoidance of both foods and air born indoor allergens have shown a persisting reduction of asthma. Importantly, the development of allergy to environmental allergens is a complex gene-environment interaction and some susceptible/predisposed individuals may benefit from reduction of allergen exposure. Further studies on the influence of both genetic and environmental factors are warranted. The present recommendations for primary prevention of allergic diseases are shown in Table 6 and 7.

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7 THE ROLE OF MICROBIOME

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KEY MESSAGES

- The number of microorganisms living in and on our body surfaces outnumbers human cells by a factor of 10
- The microbiome is essential for a healthy immune response
- The gut microbiome plays an important role in protecting from the development of allergic airway disease in mice
- Exposure to a rich and diverse microbial environment such as seen on traditional farms protects from allergic diseases

All plants, animals and humans live in close association with microbial organisms. Historically, microbiologists have isolated and grown microorganisms to identify pathogens causing disease. The advent of DNA based sequencing methods has allowed amplification of DNA from microorganisms and thereby identification of a large variety of microorganisms that have never been cultured before. The Human Microbiome Project has shown that the human body contains trillions of microorganisms, which outnumber human cells by 10 to 1 (Figure 1). Their genes encode products essential for human survival. In the gastro-intestinal tract microbes break down many of the proteins, lipids and carbohydrates from our diet into nutrients so that we can absorb them. Moreover, microbes produce beneficial compounds such as vitamins. The microbiome also profoundly affects the host's immune response. Mice raised under germ-free conditions have profound deficits in innate and adaptive immunity suggesting that the microbiome educates a child's immune system.

Experimental studies in mice, furthermore suggest that the microbiome has a role for the development of allergic diseases. Germ free mice develop more easily allergic asthma than conventionally raised mice. Reconstitution of neonates—but not adult—germ free mice with a conventional microbiota protected the animals from allergic disease. This protective effect may be mediated by activation of immune responses by microbial compounds. Alternatively or additionally metabolites secreted by microbes such as short-chain fatty acids may mediate these beneficial effects. Changes in the microbiome will occur with diet and antibiotics as long as they are ingested. But also microbial exposures in the environment will affect the microbiome and thereby the risk of allergic diseases.

Children being raised in environments rich in microbial exposures such as on traditional farms (Figure 2) have a much lower prevalence of asthma, hay fever and allergic sensitization as children grown up in urban settings. The diversity of the microbial exposure has been shown to account for the asthma-protective farm effect (Figure 3). In urban areas high exposure to environmental microbes (e.g. by keeping dogs indoors) also relates to a lower prevalence of allergic disease. A recent mouse study has demonstrated the pivotal role of the gut microbiome in mediating this protective environmental exposure. Some birth cohort studies also suggest that the composition of the gut microbiota may be a predictor for the onset of atopic eczema in young children, but these observations are not consistent and need further confirmation.

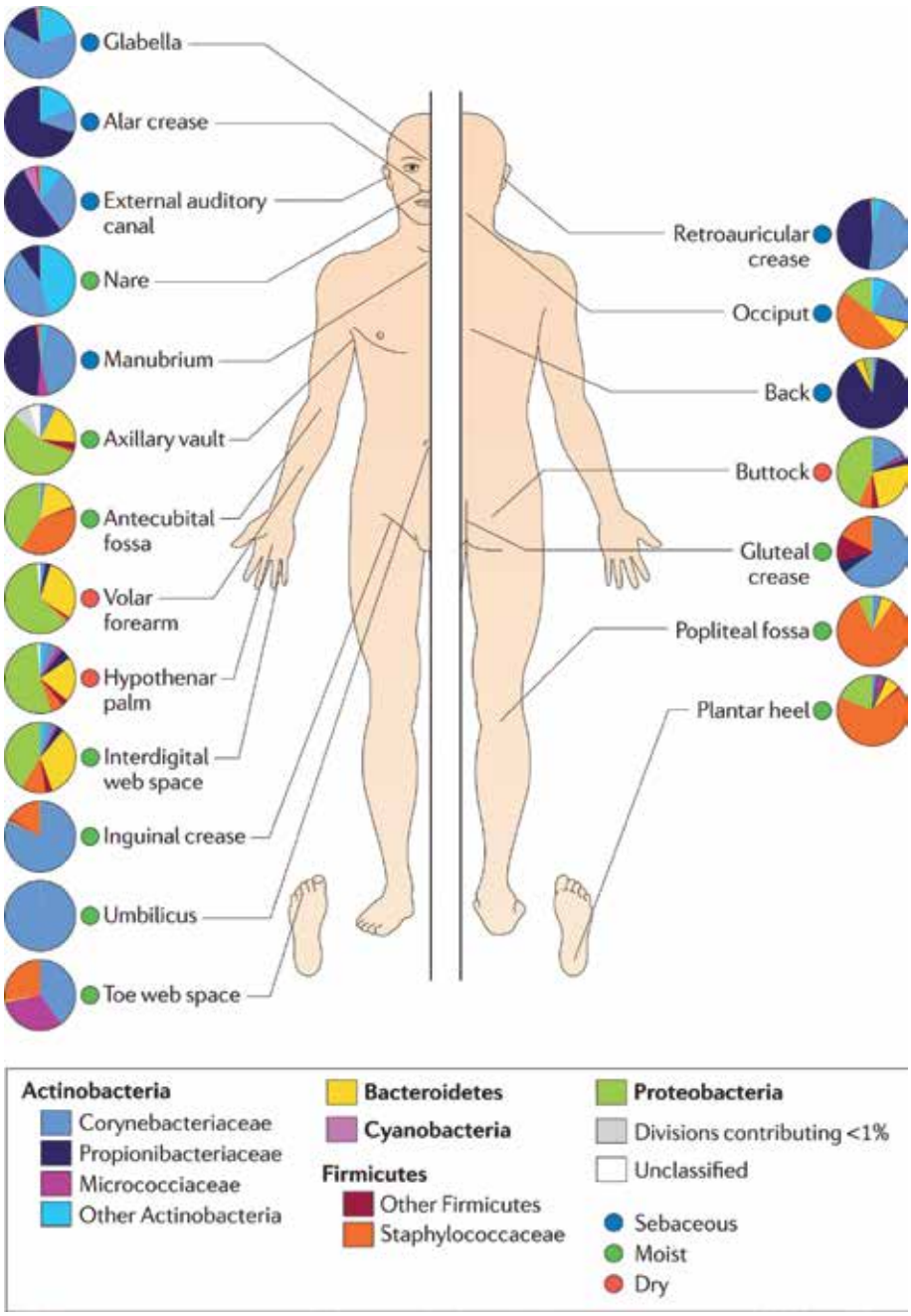

Figure 1 The diversity of the skin microbiome at different anatomical areas. (*Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Microbiol, Grice EA1, Segre JA, The skin microbiome, 9,244-253, copyright 2011.*)

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Figure 2 Protection from childhood asthma and allergies has been shown for young children growing up on traditional farms rich in microbial exposures in the environment.

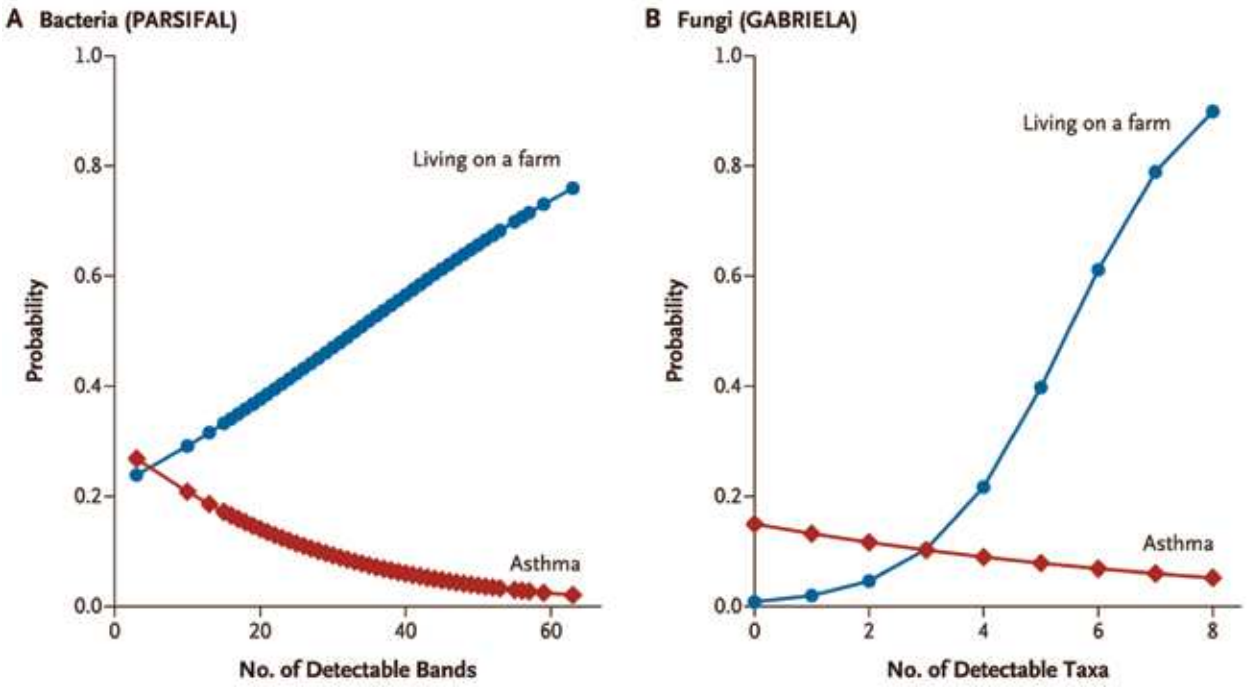

Figure 3 The diversity of bacterial and fungal exposure in the environment protects from childhood asthma. (*From New Engl J Med, Ege MJ, Mayer M, Normand AC, et al. Exposure to environmental microorganisms and childhood asthma,364,701-9, Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.*)

Section C

ALLERGY DIAGNOSIS

* Skin tests
* Nasal and bronchial provocation tests
* Food provocation tests
* In vivo diagnosis of NSAID hypersensitivity (Aspirin provocation tests)
* Drug provocation tests
* The allergen challenge chamber
* Allergen- specific IgE
* Molecules and component-resolved diagnosis
* Cellular allergy testing
* Biomarkers for allergy diagnosis and treatment

1 IN VIVO ALLERGY DIAGNOSIS - SKIN TESTS

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Skin tests are an important diagnostic tool in the work up of many allergic diseases (Table 1). Skin tests are widely used for the diagnosis of inhalant allergies, but also allergies to foods, venom, occupational agents and drugs can be investigated by skin tests.

KEY MESSAGES

- Skin tests are a cornerstone in the diagnosis of allergic diseases
- Performing skin tests needs a specific training
- Skin Prick Tests are an excellent tool to detect sensitizations to inhalant and food allergens
- Intradermal tests are of paramount importance in venom and drug hypersensitivity

TYPES OF SKIN TESTS AND REQUIREMENTS

Skin prick tests (SPTs) and intradermal tests are still the cornerstone of the diagnosis of IgE-mediated (type I) allergy. Especially SPTs are widely used (Figure 1). As they are usually easy to perform, cheap and allow a fast reading, they are an ideal tool for bedside diagnosis. Intradermal also named intracutaneous testing (Figure 2) is more demanding, but allows by titration of various allergen concentrations a very accurate rating of the sensitization level.

Epicutaneous or patch tests are used in patients with suspected type IV allergies for contact dermatitis or delayed type of drug hypersensitivity. Due to its potentially scar-inducing effect skin testing by scratching is limited to some special aspects of drug or mostly occupational allergens. The atopy patch tests (APT) may help to find out causes of exacerbation in atopic dermatitis or Eosinophilic Esophagitis, but its value is still controversial. Performing skin tests needs a specific training, especially for intradermal and epicutaneous tests with nonstandardized allergen material.

Contraindications such as the use of some drugs, pregnancy or other conditions precluding some types of allergy testing should be evaluated. Also the skin condition of the patient must allow testing in the skin. Patients have to abstain from medications such as antihistaminics that could mask a positive type I reactions; on the other hand conditions such as dermographism/pressure urticaria able to provoke false positive skin reactions must be considered. Using controls such as histamine for positive and saline as negative controls are crucial for SPT/intradermal testing.

SKIN TESTS FOR INHALANT ALLERGENS

SPT are the classical diagnostic tool get prompt information about sensitizations against inhalant allergens such as pollen, house dust mites, pets and, to a lesser extent moulds. As they are usually easy to perform, cheap and allow a fast reading, thus an ideal tool for bedside diagnosis. Recommendations for standard series of SPT solutions are available for many geographic and climatic regions.

Skin prick tests can also be used in tropical areas and in countries with limited resources, where allergy is booming. However, local allergens may not necessarily be identified or available and can therefore be missed for skin testing. For example, it is crucial to include allergens such as *Blomia tropicalis* in the skin test battery of tropical countries.

TABLE 1

Difference between basophils and mast cells

	Skin Prick Test	Intradermal Tests	Epicutaneous (Patch) Tests	Atopy Patch Test
Inhalant allergies	+++ Standard	Rarely needed, few available allergens	n.a.	Some forms of atopic dermatitis[1]
Food allergy	++ With commercially available extracts and fresh food	n.a.	n.a.	Eosinophilic esophagitis? Some forms of atopic dermatitis[2]
Venom allergy	+ (reduced sensitivity)	+++ (Titration)	n.a.	n.a.
Drug hypersenstivity	+ to ++	+++ (with all soluble drugs; Titration)	(++) In delayed drug hypersensitivity[3]	n.a.
Contact allergens	(+) (in case of protein contact dermatitis)	n.a.	+++	

[1] *If Atopic Dermatitis seems to exacerbated by the presence of inhalant allergens*
[2] *If Atopic Dermatitis seems to exacerbated by the presence of food allergens*
[3] *Especially if cutaneous manifestations of delayed type (eczema,maculo-papular rash) occur*

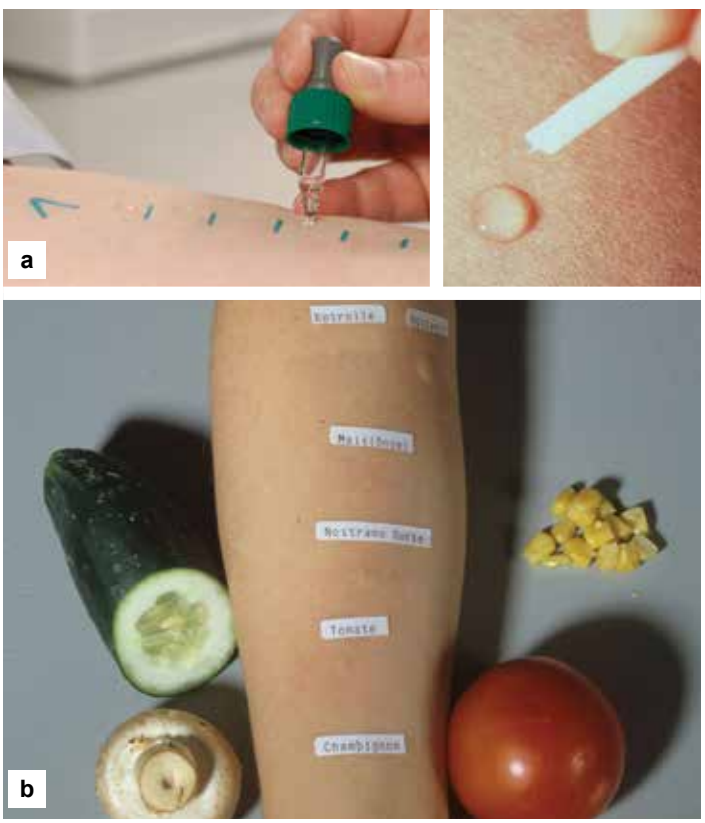

Figure 1 Skin prick test with a) inhalant allergens and b) fresh food.

Figure 2 Intradermal testing with venom (Honey bee) in different concentrations (titration).

SKIN TESTS FOR FOOD ALLERGY

For food allergy mostly SPT is used, done with commercially available food allergen extracts but also with fresh food (Prick-to Prick technique, Figure 1b). Testing with fresh food enables a fast detection of sensitization also to foods individually provided by the patient or only locally available. As skin testing does not discriminate between sensitization and clinical relevant food allergy, additional tools such as food allergen oral provocation tests, elimination diets and more recently component-resolved in vitro diagnosis are indicated. Intradermal testing with food allergens is not recommended.

SKIN TESTS FOR HYMENOPTERA VENOM ALLERGY

Skin testing for hymenoptera venom allergy is a very reliable and useful diagnostic tool. While SPT with venoms has limited sensitivity, intradermal testing with increasing concentrations allows the detection of the sensitization threshold, with high sensitivity and specificity. Concentrations starting at 0.00001 µg/ml with a ten-fold increase in doses at each step till 1.0 µg/ml are used. Simultaneous testing with two hymenoptera venoms seems to be safe and allows fast bed-side diagnosis.

SKIN TESTS IN DRUG HYPERSENSITIVITY

Skin tests are a very useful but also delicate tool to investigate drug hypersensitivity. Especially for intradermal testing of soluble drugs, the ideal concentrations need to be evaluated. In a recent position paper of the ENDA/EAACI Drug Allergy Interest Group drug concentration for skin testing aiming to achieve a specificity of at least 95% have been postulated. Currently such drug concentration can be recommended for beta-lactam antibiotics, perioperative drugs, heparins, platinum salts and contrast media. For many other drugs, there is still insufficient evidence to define an appropriate drug concentration.

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2a IN VIVO ALLERGY DIAGNOSIS- NASAL AND BRONCHIAL PROVOCATION TESTS

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KEY MESSAGES

- Nasal and bronchial provocation tests are of additional value in the understanding and diagnosis of allergic rhinitis and asthma
- These tests need to be performed in a clinical setting by dedicated staff
- It is strongly recommended to follow a validated and standardized protocol
- In experienced hands, the safety risks of challenge tests are low

INTRODUCTION

Epidemiological studies have shown that inhaled allergens are an important cause of allergic rhinitis (AR) and asthma. Allergen inhalation challenge mimics the natural situation and is useful for understanding the mechanisms of allergic airway inflammation and airway hyperresponsiveness (AHR). Moreover, provocation tests play an important role in the diagnosis of asthma, and to a lesser extent also in AR. Via a bronchial provocation test (BPT), AHR can be measured by challenging the airways with a variety of physical and inhaled chemical stimuli resulting in airway constriction (Figure 1). The airway narrowing is measured by changes in FEV1 after gradually increasing the dose of provoking agent.

A nasal provocation test (NPT) is used in case of a typical history of AR and a negative allergy test (Figure 2). It is of importance to differentiate AR from non-allergic rhinitis since management may be different. A positive test result is defined by the presence of symptoms typical for AR plus objective parameters, such as decreased upper airway patency (measured with acoustic rhinometry or anterior rhinomanometry) or nasal secretion of inflammatory mediators. Patients can have immediate or dual responses.

METHODS

Different methods for NPT and measurement of nasal responses are used. Medication that may interfere with the results should be stopped prior to the test and contra-indications should be ruled out. If available, it is advised to follow a validated and standardized protocol.

Inhaled allergen challenge starts early in the morning in order to measure a late asthmatic response. Ideally, patients are observed for a longer period. It is strongly recommended to perform BPT in a clinical setting. In daily clinical practice for AHR diagnosis, the preferred agents are histamine, methacholine and mannitol. These agents give a bronchoconstrive response that is less prolonged and quickly reversible with bronchodilators and inhaled corticosteroids. Diagnosis of occupational asthma and rhinitis may require specific inhalation tests.

LIMITATIONS

Inhaled allergen provocation tests are safe in a dedicated setting with experienced staff. Several objective and validated parameters to measure response are available for BPT, but not for NPT. Allergen application may produce nonspecific reactions. A limited number of standardized allergen extracts are commercially available. Allergen challenge can result in a transient increase in symptoms and medication use.

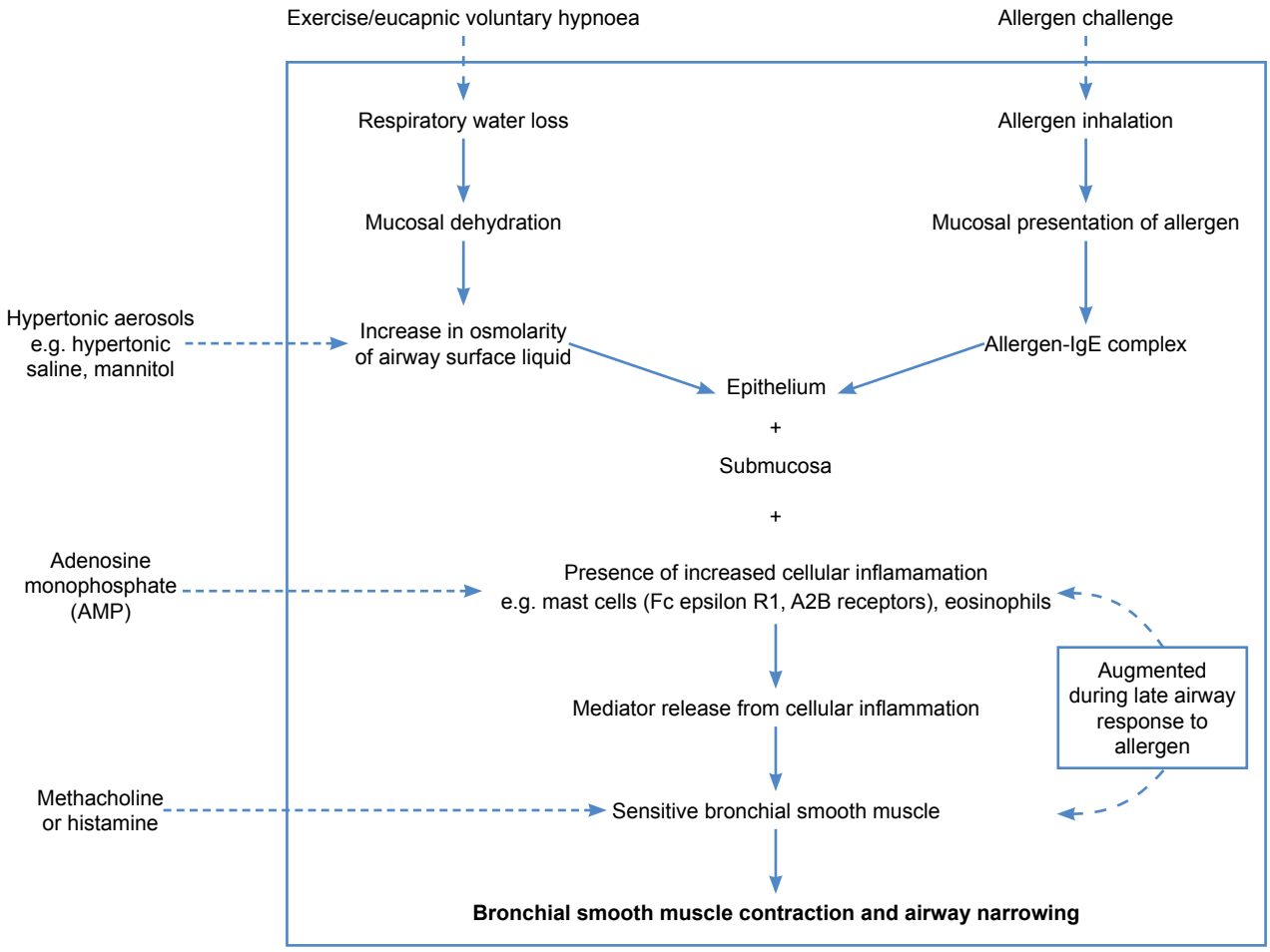

Figure 1 Mechanism of action in bronchial provocation tests. (*Reproduced with permission from O'Byrne PM, Gauvreau GM, Brannan JD. Provoked models of asthma: what have we learnt? Clin Exp Allergy 2009;39:181-92, with permission from Willey Blackwell.*)

TABLE 1

Indications for NPT or BPT
• To confirm a diagnosis of occupational allergic rhinitis or asthma.
• Discrepancy between history and routine diagnostic procedures.
• To confirm a diagnosis in a patient who has difficulty accepting the consequences of disease, such as avoiding pets or changing jobs.
• To study pathophysiological mechanisms and pharmacological efficacy of medication

TABLE 2

Contra-indications for NPT or BPT
• Advanced nasal polyposis (NPT)
• A recent history of nasal surgery (NPT)
• Respiratory tract infection in the last 2 weeks.
• Instable asthma (BPT)
• FEV1 < 70% of predicted (BPT)
• Pregnancy
• Recent vaccination (< 1 week)
• Use of systemic Beta-blockers

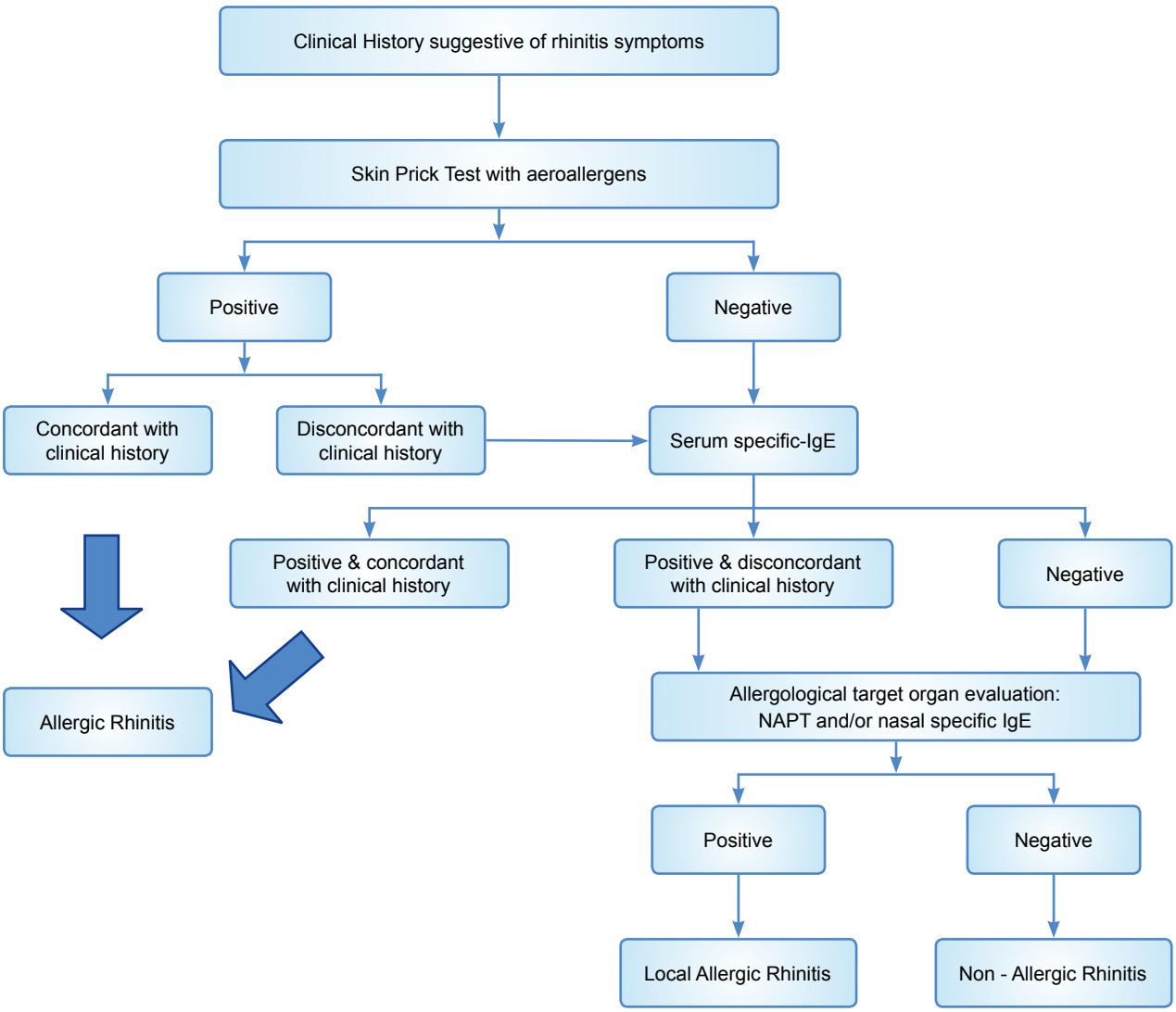

Figure 2 Diagnostic approach to the patient with allergic rhinitis. (*Reprinted from J Allergy Clin Immunol, 129/6, Rondon C, Campo P, Togias A, et al. Local allergic rhinitis: concept, pathophysiology, and management, 1460-1467, Copyright 2012, with permission from Elsevier.*)

SAFETY AND SIDE EFFECTS

NPT and BPT are safe procedures. Generalized reactions are rare after BPT, but asthma exacerbations may occur. After allergen challenge the magnitude of the bronchoconstriction may be more difficult to control than with direct challenges, such as histamine or methacholine. Moreover, the induced bronchoconstriction is usually prolonged due to the release of proinflammatory mediators. Therefore, it is necessary that during an inhaled allergen provocation a doctor is present, the rescue medication is ready to use and a resuscitation set is available on the ward.

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2b IN-VIVO ALLERGY DIAGNOSIS- FOOD PROVOCATION TESTS

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KEY MESSAGES

- Food challenge is the diagnostic gold standard for food allergy since the presence of atopy in an individual might lead to false positive interpretation of IgE testing
- Patient safety is key to the design of a food challenge
- Interpreting a food provocation test can be challenging, the experience of the staff is decisive
- Food challenges are essential procedures in the follow-up of food allergy

WHY DO WE DO FOOD CHALLENGES?

Diagnosis of food allergy can be obvious, for example in the case of a child reacting with urticaria 10 minutes after having eaten peanuts. In this case caused by an IgE-mediated reaction, skin prick tests and in-vitro diagnosis, by measuring specific IgE in the serum, are most often positive and clearly relate to the symptoms. Food challenge might be done in patients with vague symptoms possibly related to food allergy, with a significant proportion of patients having positive IgE tests not related to the symptoms but to an atopic predisposition (false positive tests indicating only sensitization). In this context, a food challenge will be the gold standard for diagnosis (Figure 1).

HOW DO WE DO FOOD CHALLENGES?

Several variables have to be taken into account when organizing a food challenge. Most importantly, the food challenge must be designed in a safe way. The food challenge must be performed in a location, where emergency medication can be administered. When doing high risk challenges, it is important to have rapid access to intensive care facilities. In all cases, the food challenge must be supervised by nurses trained to recognize early signs of reactions. Also, the supervising physician must be trained in order to have sufficient experience in interpreting the various clinical signs possibly observed during a food challenge.

The food is provided to the patient in increasing doses. The starting dose, as well as the time interval between the doses, will be determined by the initial history of the patient and by the purpose of the challenge. A food challenge aiming to determine the threshold level of a reaction will start with a very low dose.

The food can be administered openly, but also in a double-blind placebo controlled manner. During this procedure, the challenge is separated into two parts, the food being hidden in a vehicle in order for blind both the patient and the examiner (Figure 2).

LIMITATIONS OF A FOOD CHALLENGE

A well designed food challenge will provide definite information about the presence or the absence of a food allergy. Nevertheless, one needs to be aware of some caveats. A food challenge is valid only for the type of preparation of the food. As an example, patients may react to raw egg, but not to cooked egg, and a patient with a negative challenge to cooked egg might afterwards react to a preparation with raw or not completely cooked egg. Similarly, a negative challenge to a specific fish does

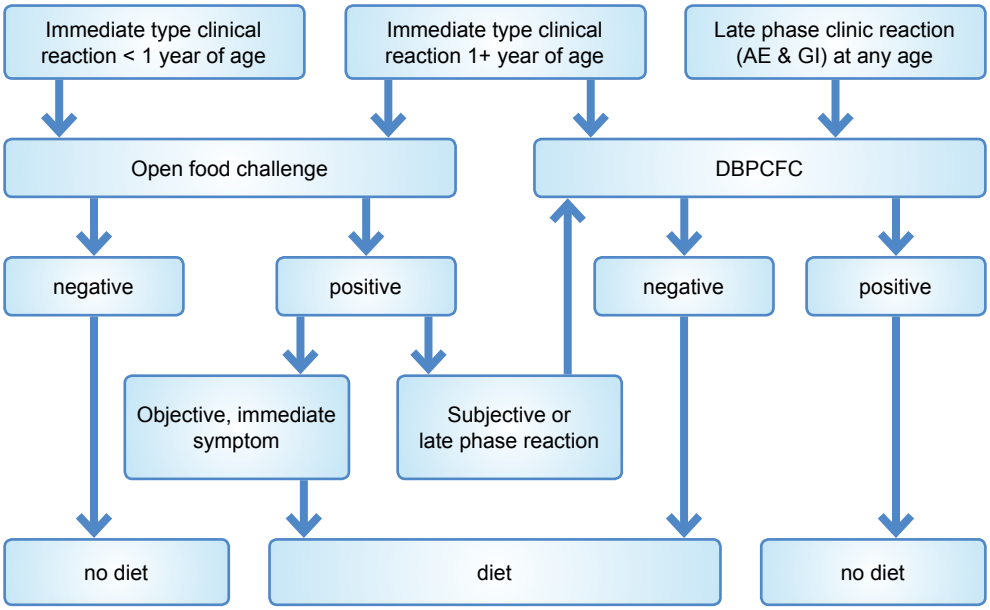

Figure 1 Decision tree for food allergy including either an open food challenge, or a double-blind, placebo-controlled food challenge (DBPCFC). (*Reproduced with permission from Niggemann B and Beyer K. Diagnosis of food allergy in children: toward a standardization of food challengeJ Pediatr Gastroenterol Nutr 2007, 45, 399-404.*)

Figure 2 Pastry containing a peanut butter or placebo cream prepared for a double-blind, placebo-controlled food challenge to peanuts.

not indicate that the patient can eat all types of fish.

A well designed food challenge is the definite diagnostic tool for food allergy. In addition, it is also a very useful tool in the follow-up of food allergic patients. A positive food challenge provides valuable information to the patient on how the reaction could take place and how to treat it, thus increasing the patient's quality of life.

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2c IN VIVO DIAGNOSIS OF NSAID HYPERSENSITIVITY

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KEY MESSAGES

- Aspirin (ASA) challenge tests are performed to confirm history of ASA hypersensitivity or to confirm/exclude cross-reactivity
- Oral provocation test (OPT) with ASA is the gold standard, but may be substituted by inhaled or intranasal challenge with lysine-ASA in patients with respiratory type of reaction to non-steroidal anti-inflammatory drugs (NSAIDs)
- OPT can be also used for testing hypersensivity to other culprit NSAIDs or to assess tolerance to an alternative NSAIDs

Oral provocation test (OPT) with aspirin (ASA) is the gold standard for the diagnosis of cross-reactive types of hypersensitivity to NSAIDs, which include NSAIDs-exacerbated respiratory disease (NERD), NSAIDs-exacerbated cutaneous diseases (NECD) and NSAIDs-induced angioedema/urticaria. In patients with single NSAIDs induced type of reactions, ASA is rarely a culprit drug, so OPT with the suspected NSAID may be performed. In patients with NERD, bronchial or nasal challenges with the soluble form of ASA (lysine-ASA) may be an alternative to OPT to confirm/exclude NSAIDs hypersensitivity.

ORAL PROVOCATION TEST

Oral challenge with ASA is recommended in patients with suspected respiratory or cutaneous form of reactions to NSAIDs. Appropriate safety measures should be followed and contraindications considered (Table 1). In patients with NERD, the two day protocol starts with placebo capsules administered on the first day, every 1.5-2 hours, with FEV1 measured every 30 minutes to establish baseline variability (Table 2). On the second day, the patient receives initially 10-30 mg of aspirin and the dose is doubled at 1.5 hours intervals, until a positive reaction occurs, defined by at least 20% fall in FEV1 and /or extra-bronchial symptoms (nasal or ocular congestion, rhinorrhea, erythema of the skin, gastro-intestinal symptoms). The test is negative if none of the above appears and the final ingested dose of 312 mg of ASA is well tolerated. A similar protocol, with extended intervals between ASA doses is indicated for the diagnosis of the cutaneous type of NSAIDs hypersensitivity (Table 3).

TESTING WITH OTHER NSAIDS

OPT can be used for testing hypersensitivity to other culprit NSAIDs or to assess tolerance to an alternative NSAIDs in patients with both cross-reactive and immunologically-mediated reactions. Even if no immediate indications for treatment with NSAIDs exist, the potential patient's need for an analgesic, antipyretic or anti-inflammatory treatment should be anticipated. Tests with alternative NSAIDs usually start with the oral administration of half of the therapeutic dose followed by monitoring in the doctor's office up to two hours.

INHALATION PROVOCATION TEST

In patients with NERD, inhalation or intranasal challenge with Lysine (L)-ASA (a soluble form of acetylsalicylic acid) can be used as an alternative to ASA-OPT (Figure 1)

The bronchial provocation test start with the inhalation of a diluent, followed by increasing doses of L-ASA administered using

TABLE 1

Indications and contra indications to oral aspirin challenge in patients with NSAIDs hypersensitivity
Indications
• Ambiguous or not clear history of response to aspirin/NSAIDs
• Confirmation/exclusion of cross-sensitivity if aspirin is not a culprit NSAID
• Beginning of desensitization
Contraindications
• History of severe anaphylactic reactions induced by aspirin or other NSAIDs
• Not well controlled underlying disease (asthma/urticaria)
• Low baseline FEV1 (below 70% of the predicted value)
• Severe delayed type reactions
• Concomitant disorders potentially aggravated by the challenge

TABLE 2

Protocol for the oral aspirin challenge in a patient with suspected NSAIDs exacerbated respiratory diseases		
8:00	Placebo	10 mg[a]
9:30	Placebo	27 mg
11:00	Placebo	44 mg
12:30	Placebo	117 mg
14:00		312 mg

[a] *Optional in patients with a history of severe reaction to NSAIDs*

TABLE 3

Protocol for oral aspirin challenge in a patient with suspected NSAIDs exacerbated cutaneous disease		
Time	Day 1	Day 2
8:00	Placebo	71 mg
10:00	Placebo	117 mg
12:00	Placebo	312 mg
14:00	Placebo	500 mg

a dosimeter at 30 minutes intervals, allowing to complete the procedure in an outpatient setting in less than 5 hours. The test is considered positive, if at least 20% drop in FEV1 is recorded at 10, 20 or 30 minutes after inhalation. If the positive reaction is observed PD20 ASA is calculated from the dose-response curve. Inhalation challenge may induce extrabronchial symptoms and may also involve a late phase reaction. Both oral and inhaled tests have similar sensitivity and specificity but, as compared to the oral challenge, the inhalation test, is faster and safer to perform (the reaction is usually easily reversible with nebulized beta2 agonists).

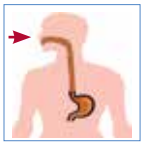
		Advantages	Limitations
Oral challenge		Gold standard (reliable)	Risk of severe reaction
		Useful in patients with extra bronchial symptoms	Time-consuming
Bronchial challenge		Short duration (< 4 h)	Only in patients with bronchial/nasal symptoms
		Reaction easily reversible	Requires special equipment (dosimeter)
Nasal challenge		Safe in patients with severe/ unstable asthma	Only in patients with bronchial/nasal symptoms
			Not possible in patients with nasal obstruction

Figure 1 Advantages and limitations of oral, bronchial and intranasal route of aspirin challenge in patients with NSAIDs- exacerbated respiratory disease.

The nasal provocation test with L-ASA is particularly recommended in asthmatic patients with low pulmonary function not suitable for bronchial provocation. The challenge starts with instillation of saline followed by L-ASA solution increasing concentrations applied into each nostril every 30 minutes. All parameters (objective and subjective) are recorded every 10 minutes. Alternatively, ketorolac nasal spray solution can be used. For the assessment of the challenge, clinical symptoms are combined with the objective measures of nasal airflow patency (acoustic rhinometry, rhinomanometry or peak nasal inspiratory flow).

The reaction is considered positive, if clinical symptoms appear and/or a significant nasal obstruction is objectively documented (a 25% decrease in total nasal flow or 40% drop of the inspiratory nasal flow, as compared to baseline).

In experienced hands the sensitivity of intranasal aspirin provocation may rise above 80% and specificity approaches 95%, thus reaching the performance of the bronchial challenge.

The nasal challenge route is not recommended in patients with significant nasal obstruction, turbulent nasal flow or with unspecific nasal responsiveness.

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2d

IN VIVO ALLERGY DIAGNOSIS - DRUG PROVOCATION TEST

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KEY MESSAGES

- For many drug hypersensitivity reactions, no sensitization can be demonstrated
- A drug provocation test is the controlled administration of a drug for diagnostic purposes
- It is the golden standard to confirm or exclude drug hypersensitivity
- Specific protocols are available for several drugs
- A drug provocation test is often the only reliable way to establish a diagnosis and should be considered after risk-benefit analysis

BACKGROUND AND INDICATIONS

A drug hypersensitivity (DH) reaction is particularly difficult to prove, as the history may be unreliable and for many drugs and reactions no sensitization can be demonstrated by skin tests or in-vitro tests. A drug provocation test (DPT) is performed: a) to exclude DH in a non-suggestive history (e.g. unspecific symptoms arising after intake of a penicillin), b) if a cross-reactivity in proven hypersensitivity has to be excluded (e.g. to other pain medications in acetylsalicylic acid hypersensitivity), c) if a firm diagnosis in suggestive history of DH with negative, non-conclusive or non-available allergological tests shall be established (Table1). It is considered to be the gold standard for DH diagnosis, required when other allergy tests do not allow relevant conclusions.

PROCEDURE

A drug provocation test (DPT) is the controlled administration of a drug for diagnostic purposes, performed under close medical surveillance with emergency medication available and always after an individual risk-benefit analysis. Requirements for a DPT include the possibility to hospitalize patients, experience with emergency treatment, consideration of pharmacological effects of tested drugs, exclusion of contraindications, informed consent of the patient and sufficient wash-out interval from anti-allergic medication. It is a high risk procedure as it induces symptoms similar to the original ones, albeit normally milder because of initially low and fractionated doses and immediate treatment (Figure 1, Table 2).

The oral provocation test is the preferred route for most DPTs, although subcutaneous (e.g. for local anaesthetics, heparins, insulins), local or even intravenous provocations (e.g. for heparin) are possible. The time interval between dose escalations and the

Figure 1 Mild generalized acute urticaria after oral drug provocation test with 500 mg acetylsalicylic acid (as in Aspirin®) in a patient with reported drug hypersensitivity to another potentially cross-reacting pain medication.

TABLE 1

Indications for a drug provocation test
• To exclude hypersensitivity in non-suggestive history of drug hypersensitivity
• To exclude cross-reactivity of related drugs in proven hypersensitivity
• To establish a firm diagnosis in suggestive history of drug hypersensitivity with negative, non-conclusive or non-available allergological tests
• Validation of the history and other allergological tests (reference standard)

Modified from Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003;58: 854-863.

TABLE 2

Clinical reactions to drug provocation tests in 241 patients with confirmed drug hypersensitivity	
Manifestation	**Number (Percentage)**
Urticaria	160 (66.4%)
Maculopapular exanthema	22 (9.1%)
Bronchospasm	9 (7.9%)
Laryngeal edema	10 (4.1%)
Anaphylaxis without shock	17 (7%)
Anaphylatic shock	13 (5.4%)

duration of provocation have to be determined considering the original reaction and suspected mechanism.

General guidelines for performing DPT have been published and specific protocols are available for some drugs, such as betalactam drugs, nonsteroidal anti-inflammatory drugs or radiocontrast media.

INTERPRETATION

In the majority of patients, DH can be excluded by DPT. In some patients, the reappearance of reactions confirms the diagnosis. False positive and false negative results to DPTs are possible. In medicine, a DPT can never guarantee tolerance in 100% of patients, but helps to decide, if lifelong avoidance is justified. Studies evaluating the validity of the DPT show that the majority of patients (>95%) tolerated the drug in real life, if there were no reaction in the DPT and conclude that this test is beneficial for the patient.

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2e THE ALLERGEN CHALLENGE CHAMBER

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KEY MESSAGES

- A challenge in the allergen challenge chamber (ACC) affects several target organs of type I allergy
- A stable and reproducible allergen load in the ACC is the basis for consistent subjective symptom scores
- Challenge sessions with comparable meaningful results are possible all over the year
- ACC enables to obtain objective parameters supporting subjective symptom scores
- ACC can monitor specific immunotherapy and pharmacotherapy
- ACC can reduce the cost of drug development

In contrast to several other provocation tests, allergen challenge chamber (ACC) tests are not focused on single organs, but on several targets of type I allergic reactions like eyes, upper and lower respiratory tract and even skin. In contrast to other allergy tests, ACCs are usually not applied for individual diagnosis, but for assessing allergic treatments, studies in occupational allergy and basic research.

At present, there are twelve ACCs active in Europe, USA, Canada and Japan (Figure 1). There is a broad conformity between the systems, although individual differences are to be mentioned. All ACCs are validated for pollen challenges like grass/ birch/ragweed or Japanese cedar pollen; some are also validated for house dust mite or even for cat (Figure 2).

The main common feature of all ACCs is a pre-defined and stable allergen concentration in the air, which has to be high enough to induce symptoms in sensitized subjects. In addition, the allergen concentration climatic conditions like temperature, humidity and CO2 concentration are kept stable over several hours. All parameters are constantly controlled to ensure high reproducibility of the ACC model. During a challenge session patients record their subjective symptoms several times an hour with good compliance. There is usually no application of rescue medication, which could possibly complicate the interpretation of the symptom score. Usually nasal, ocular and/or bronchial symptoms are scored using a 4-point scale (0 to 3).

A challenge session lasts at least two hours, because by then a plateau is normally reached in all of the patients' symptoms, which will then not vary, if the allergen load is kept stable. This plateau-reaction is usually monitored for two to six hours (Figure 3).

In contrast to field or park studies, it is possible to additionally monitor and report objective assessments during the challenge sessions. These objective parameters offer the opportunity to check the properness and accuracy of the subjective scoring (Table 1). Furthermore, it is possible to take blood samples at several time points of the challenge session to follow the ongoing allergic reaction.

The ACC model is approved by the FDA and EMA, at least for phase II trials and further supporting phase III trials. EMA suggests ACC trials for conducting dose finding trials of immunotherapeutic products. Potential fields of application of ACC trials, however, can be more extensive (Table 2).

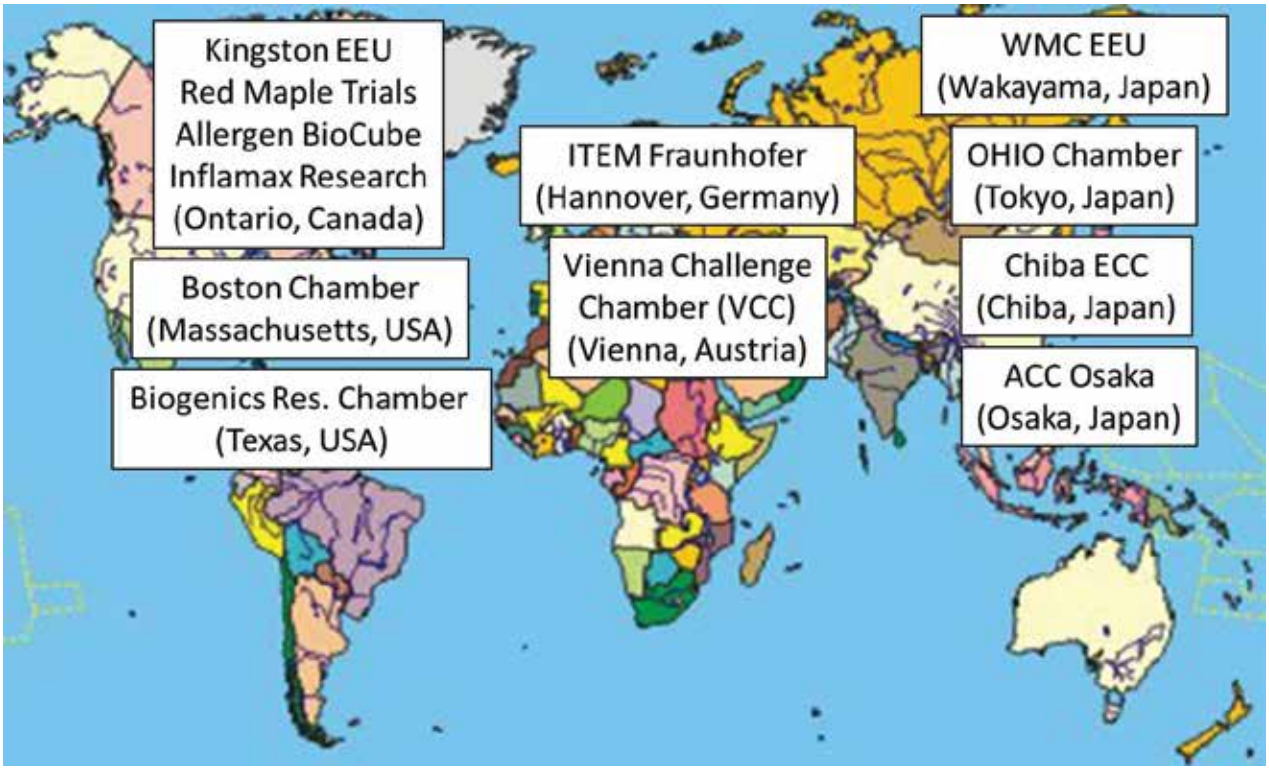

Figure 1 Distribution of Allergen Challenge Chambers in the World.

Figure 2 The Vienna Challenge Chamber (VCC)

ACC can monitor specific immunotherapy and reduce the cost of drug development substantially, not only by proof of concept studies. Requiring significantly less time than field studies and smaller numbers of individuals per trial are the essential arguments for application of ACCs. Besides several advantages some disadvantages are to be mentioned (Table 3). The standardization of several ACCs worldwide and the "between-unit" reproducibility are still unmet targets.

TABLE 1

Objective assessments performed in an ACC
Rhinomanometry
Spirometry
Peak Expiratory Flow (PEF)
Nasal secretion weight
Nasal scraping
Nasal lavage
Nasal Peak Inspiratory Flow (NPIF)
Slit lamp investigation
Conjunctival imaging
Digital Endoscopy
Acoustic rhinometry
Blood samples (drug level, mediators,...)

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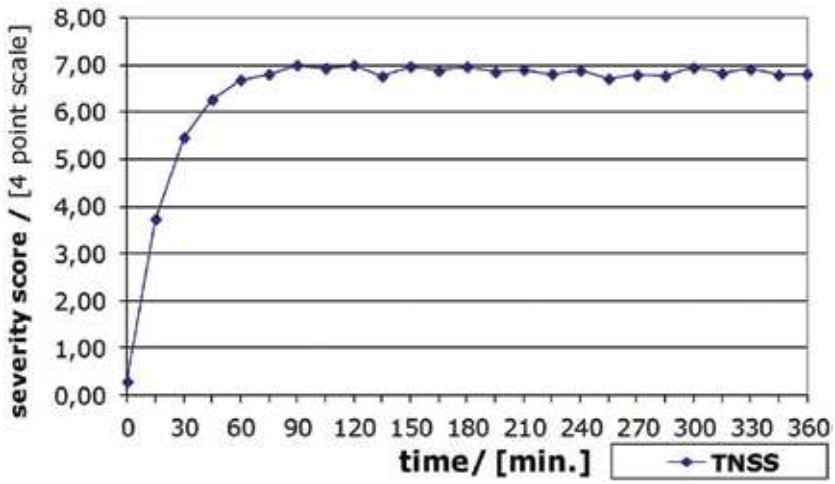

Figure 3 Total Nasal Symptom Score (TNSS) of > 500 subjects with placebo treatment.

TABLE 2

Documented clinical trials in an ACC
Proof of concept
Dose finding
Onset of action
Magnitude and duration of action
Additive treatments
Pharmacodynamics
Pharmacokinetics
Competitive trials

TABLE 3

Possible environmental factors influencing development of allergic diseases	
Advantages	Disadvantages and unmet needs
Exposure to a defined, controlled level of allergen	Potential effects of claustrophobia or the influence of other subjects on subjective symptom scores
Out-of-season use for seasonal inhalant allergens and the ability to save up to 12 months in the development programme	Short exposure times (no more than several hours)
Rescue medication use can be prohibited or suspended during the challenge	A potentially abrupt challenge
Ability to collect biological samples from participants	Lack of seasonal priming in out-of-season challenges
Investigation of dose-ranging and onset of action	Low number of operational ACCs worldwide
Overall cost and ethical benefits due to use of lower number of subjects than in natural-exposure trials	Lack of standardization between the different ACCs in the World

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3a IN VITRO ALLERGY DIAGNOSIS – ALLERGEN-SPECIFIC IgE

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KEY MESSAGES

- Elevated serum levels of allergen-specific IgE demonstrate the atopic status of a patient and are indicative for an eventual clinically significant allergy
- Determination of allergen-specific IgE in serum allows rapid screening of the sensitization spectrum of a patient without risks for adverse reactions
- Multiplex specific IgE measurements to pure natural or recombinant allergens allow a component-resolved diagnostics, which can be useful to design a patient-tailored immunotherapeutic intervention
- For allergy diagnosis elevated allergen-specific serum IgE levels need to be interpreted in the light of clinical history. In some cases, *in vivo* provocation tests performed with the suspected allergen are needed to confirm the diagnosis

The breakthrough allowing the development of highly specific and sensitive *in vitro* tests for allergic diseases was the discovery of the "reaginic antibody" termed immunoglobulin E (IgE) more than 40 years ago. The prototype for the *in vitro* detection of serum IgE (the radioallergosorbent test, RAST) first described in 1967 used a paper disc as a solid phase to covalently immobilize the allergen followed by the addition of patient's serum. After different washing procedures to remove unbound serum proteins and antibodies, bounded IgE was detected with 125I-labelled polyclonal anti-human IgE (Figure 1). Modern assays for the detection of allergen-specific IgE have undergone impressive improvements including the calibration against the WHO Standard 72/502, allowing quantitative determinations, and the implementation of fully automated devices (Figure 2). To date the most commonly used system to determine allergen-specific IgE is the ImmunoCAP system (Thermo Fisher Scientific, Uppsala) considered as the "gold standard" for the *in vitro* diagnosis of allergic conditions. More recently, novel diagnostic tests based on allergen microarrays have been introduced both in research and clinical practice. Multiplex-based *in vitro* tools for allergy diagnosis allow a component resolved diagnostics of the atopy status of a patient in a cost effective way.

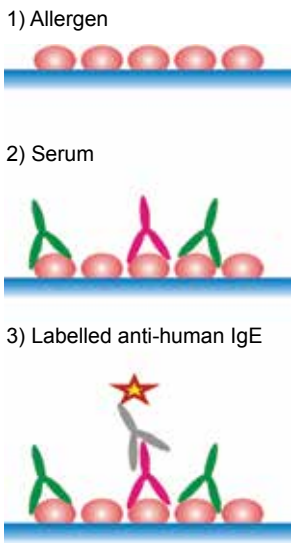

Figure 1 Typical immunoassay for the detection of allergen-specific IgE in three steps: 1) the allergen is adsorbed and immobilized to a solid phase, 2) patient's serum is added followed by incubation during 30-60 min and several washing steps and 3) allergen-bound IgE is detected by an enzymatically labelled anti-human IgE monoclonal antibody (★).

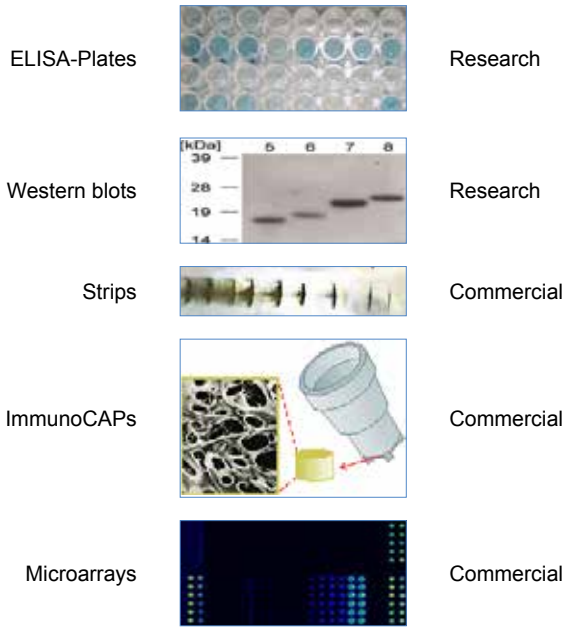

Figure 2 Most commonly used techniques for the detection of allergen-specific IgE used in research and clinics. All techniques are based on the immunoassay principle described in Figure 1.

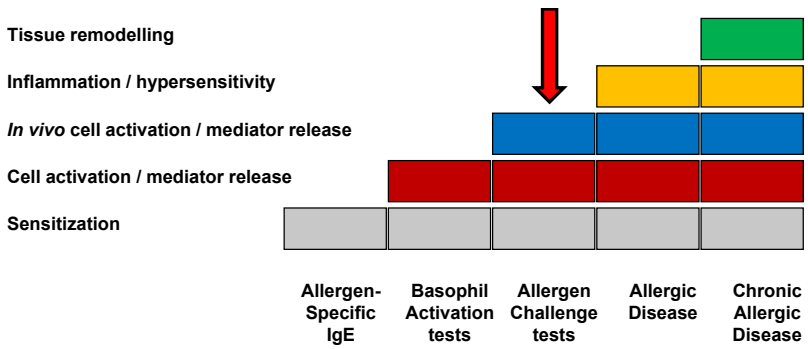

Figure 3 Steps involved in the development of allergic diseases. A switch to the production of allergen-specific IgE detectable in serum leads to the sensitization of a patient, reflecting its atopic status. However, not all sensitized individuals suffer from allergic symptoms highlighting the limitation of in vitro allergy diagnoses. Allergen challenge tests are needed to confirm the clinical relevance of an allergy suspected from the clinical history and from the presence of allergen-specific IgE in serum. (*Reproduced with permission from Bousquet J, Anto JM, Bachert C,et al. Factors responsible for differences between asymptomatic subjects and patients presenting and IgE sensitization to allergens: a GA2LEN project. Allergy 2006:61;671-680, with permission from Willey Blackwell.*)

Despite the relevant technological improvement, several problems related to the *in vitro* diagnosis of allergy remain unsolved (Figure 3). Allergen-specific IgE in serum is a marker for sensitization and a prerequisite for the development of an IgE-mediated allergy, but is not sufficient for the induction of symptoms. In fact, more than 20% of the individuals with allergen-specific serum IgE are asymptomatic. We should be aware that allergen-specific serum IgE is biologically irrelevant as long as it doesn't bind to the high affinity receptor for IgE on effector cells. Therefore, the presence or the absence of allergen-specific IgE in serum is not sufficient to confirm or exclude an allergy in all cases.

At the current state of the art, it is worthwhile to maintain a healthy scepticism about allergy diagnostic test results solely based on the determination of allergen-specific serum IgE levels and to let the clinical history, corroborated by adequate provocation tests, which drive the diagnosis before considering immunotherapeutic interventions.

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3b IN VITRO ALLERGY DIAGNOSIS – MOLECULES AND COMPONENT-RESOLVED DIAGNOSIS

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KEY MESSAGES

- The advent of molecular allergen technologies has created a shift of paradigm in diagnosing IgE-mediated allergies
- Component-resolved analysis of the specific IgE response provides a more individualized and stratified diagnosis of allergic patients
- Component-resolved diagnosis (CRD) of the specific IgE response improves the sensitivity, specificity and clinical performance of the laboratory assay
- CRD has the potential to better select patients for immunotherapy, to predict the risk for severe allergic reactions and to monitor patients for immunotherapy outcome

The history of *in vitro* (laboratory) tests for allergy diagnosis started in the early seventies, soon after the discovery of IgE in 1967. The first generation assays, starting from the very first RAST, allowed researchers and allergists to improve the diagnosis of IgE-mediated diseases. The first generation IgE assays were mainly based on allergenic extracts – a mixture of allergenic and non-allergenic compounds derived from natural sources (e.g. a pollen extract).

A great step forward to a broader use of *in vitro* diagnosis in allergy was achieved in the early nineties, when the more reliable second generation assays appeared in laboratories worldwide and in parallel a new kind of test reagent started to be available. In fact, during the nineties an increasing number of allergenic molecules have been identified, characterized and, most important, progressively translated into the daily use in diagnosis (Figure 1A). Most of the available allergenic molecules have been obtained by using the recombinant DNA technology, allowing cloning and production of recombinant allergens in a reproducible large scale. Within the last decades, allergenic molecules have been increasingly used in research and clinical studies leading to a cumulative number of scientific publications (Figure 1B).

This knowledge is now displayed in several free accessible internet-based resources documenting the magnitude of the worldwide allergy health problem (Table 1). The most recent keystone improvement in this area has been the application of microtechnology to *in vitro* diagnosis of IgE-mediated diseases. In the last decade, a new tool has become available to allergists allowing them the parallel diagnosis on hundreds of allergenic molecules from a huge collection of allergenic sources in a single test run (Figure 2). This multiplex microarray test is now available worldwide and allows allergic patients to be tested with the same panel of allergens regardless of age, gender and kind of allergen and route of exposure.

Within the last decade, multiple studies from many countries around the world independently reported an added diagnostic value by using molecular components for in vitro allergy diagnosis in the singleplex test systems – the more traditional approach in allergy laboratory testing. This progress became mainly evident in some of the most severe allergic diseases such as anaphylaxis due to food intake or insect stings, which can result in fatal outcome. Through the advent of molecular technologies, some of the weaknesses and

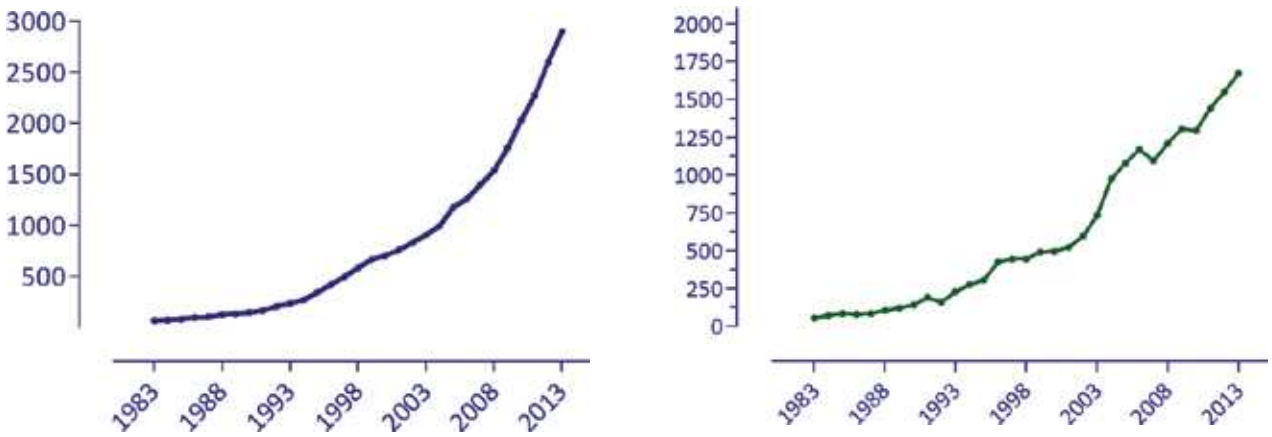

Figure 1 A - Cumulative number of identified allergenic molecules during the last three decades. (source: www.allergome.org); B - Number of scientific papers on identification, characterization and clinical use of allergenic molecules per year published in the last three decades.

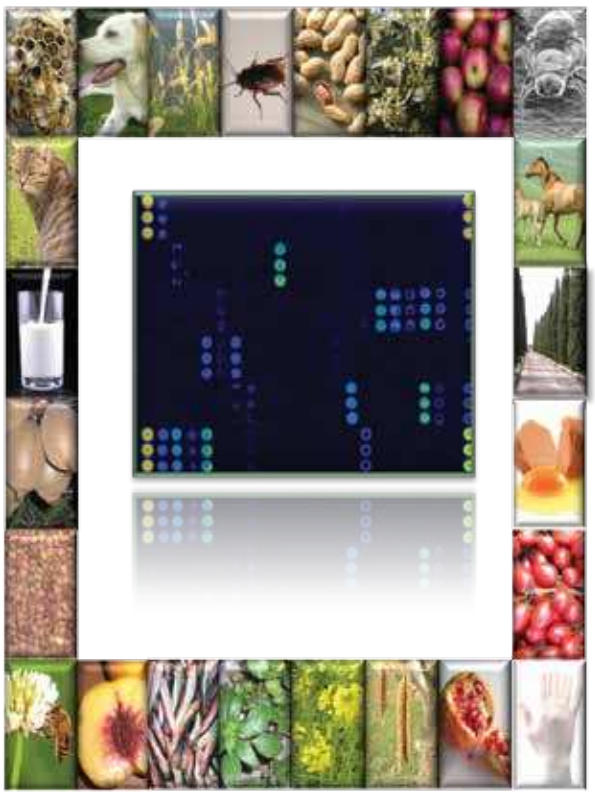

Figure 2 The new microtechnology-based tool used to detect specific IgE. Allergenic molecules, represented by proteins available as purified natural compounds or recombinants, are immobilized as microspots (200 µm in diameter) on a solid phase area of 7 x 10 mm and are grouped by sources and tissues and also on the basis of their biochemical structure and their IgE epitope sharing. It is thus possible to visualize the IgE cross-reactivity, now better-defined as IgE co-recognition, as a cluster of fluorescent spots. The extension of cluster IgE recognition can help clinical decision on whether an allergenic source must be avoided or not.

shortcomings of the classical diagnostic algorithm, which was solely based on allergenic extracts from nature, could be solved in terms of assay sensitivity, specificity and prediction of clinical severity and risk. Nowadays, several prominent examples exist, where the measurement of sIgE to molecular allergen components is a recommended state-of-the-art procedure within the algorithm for clinical decision-making (Table 2).

From a global perspective – despite the immense progress that has been achieved in the field of molecular allergy in vitro testing within the last two decades – there is a clinical and research need for a better reflection of allergenic molecules based on regional differences in the world. Not all allergens are global, some of them are regional, but still can cause severe allergic disease. This new era of allergy diagnosis, which calls for a global definition of allergenic source and molecules, has already been entered. The analysis of such wealth of data is now possible by using advanced information and communication technologies, which will ultimately result in better care for allergic patients.

TABLE 1

Comprehensive allergen databases providing free access.		
Database	**URL**	**Target/Function**
WHO/IUIS Allergen Nomenclature Sub-Committee	http://www.allergen.org/	Responsible for maintaining and developing a unique, unambiguous and systematic nomenclature for allergenic proteins
ALLERGOME	http://www.allergome.org/	A web site designed to supply information on allergenic molecules (allergens) for clinicians and researchers
AllergenOnline	http://www.allergenonline.org/	Provides access to a peer reviewed allergen list and sequence searchable database
AllFam	http://www.meduniwien.ac.at/allergens/allfam/	The AllFam database is a resource for classifying allergens into protein families (based on the Allergome website)

Abbreviations and explanations:
WHO, World Health Organization; IUIS, International Union of Immunological Societies.

TABLE 2

Molecular components or allergens with a demonstrated utility for clinical decision making in various allergic conditions			
Allergic Disease	**Molecular Component / Allergen**	**Diagnostic Problem Solved**	**Countries of Major Studies**
Insect venom anaphylaxis	Api m 1, Ves v 1, Ves v 5, Pol d 5	Better differentiation of honey bee and vespid venom double-sensitized patients	GER, SUI, AUT, SLO, USA, ITA, POL, ESP
Insect venom anaphylaxis	Ves v 5	Increased sIgE assay sensitivity through spiking of vespid venom with rVes v 5	GER, SUI, AUT
F/WDEIA	Tri a 19	Marker allergen for food-/wheat-dependent exercise-induced anaphylaxis (F/WDEIA)	JAP, FIN, DAN, GER, SUI
Peanut allergy	Ara h 2, Ara h 6	Predictive marker allergens for severe reactions to ingested peanut	USA, GBR, GER, AUS
Allergy to red meat	α-Gal	Marker allergen for delayed anaphylactic reactions to red meat and offal	USA, SWE, GER, AUT
Pollen Allergy; Insect venom anaphylaxis	CCD	Marker for broad IgE-based cross-reactivity without clinical relevance	ITA, NED, GER, AUT
Insect venom anaphylaxis	Api m 10, Api m 3	Prediction of patients at risk for therapeutic failures in honey bee venom immunotherapy	GER, SUI

Abbreviations and explanations:
Tri a 19, wheat allergen ω-5 gliadin; α-Gal, mammalian carbohydrate determinant (galactose-α-1,3-galactose); CCD, carbohydrate cross-reactive determinants (β-1,2-xylose and α-1,3-fucose); Api m 1, 3, 10, honey bee venom allergens Phospholipase A2, Acid Phosphatase, Icarapin; Ves v 1, 5, vespid venom allergens Phospholipase A1, Antigen 5; Pol d 5, Polistes venom allergen Antigen 5; Ara h 2, 6, major peanut allergens storage protein allergens.

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3c

IN VITRO ALLERGY DIAGNOSIS - CELLULAR ALLERGY TESTING

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KEY MESSAGES

- Cellular allergy tests expand the tools of the allergist to diagnose and monitor allergic disease
- The basophil activation test (BAT) documents type I sensitisation to an allergen, as fraction of blood basophils activated by soluble allergen
- Measuring basophil sensitivity as activation at graded dilutions of allergen expands the options since sensitivity to allergen is a more reproducible metric of allergic disease than provocation testing. It can be used to identify sufficiently sensitised individuals and to monitor natural and therapeutic resolution of allergy
- Identification of culprit drugs in T cell mediated Type IV drug allergy by Elispot or flow cytometry is only available at very few laboratories

Cellular allergy testing is essentially induction of the allergic response in a test tube. As any *in vitro* test, it has the advantage of quantifying the allergic response without any risk to the patient.

The most common cellular test applied is basophil activation by allergen (BAT) (Figure 1). This is used when the patient history and specific IgE or skin tests are discordant, when there is no reliable specific IgE or skin test, or if the patient history indicates that skin tests may elicit a systemic response. Determination of basophil sensitivity with serial dilutions of allergen can be used to measure the point of inflection or half maximal allergen concentration as measure of allergic response. This is a more reproducible measure of allergic disease than provocation testing. Basophil sensitivity can be used to identify food allergens, the primary sensitizer amongst cross-reacting allergens or allergen preparations and to monitor progress of allergen immunotherapy and anti-IgE therapy (Figure 2).

Basophil activation is measured as either histamine release or as upregulation of granule proteins to the cell surface in response to allergen exposure. The most common antigen to be measured on the surface of blood basophils, which are identified as CD193 or CD203c positive cells in whole blood is the tetraspannin, CD63. CD63 resides in the same vesicles as histamine in blood basophils and in tissue mast cells.

For optimal performance, introduction of basophil activation including setting up the flow cytometer should be done in the context of the existing network of units offering this service. There is a strong movement toward standardisation of measurement of basophil activation by flow cytometry, embodied amongst others by the EAACI-EuroBAT meetings and an EAACI Task Force on this topic. Contribution to and complying with standardisation will enhance the quality of this recent diagnostic tool for allergy diagnosis.

Type IV reactions to drugs can be severe and it is important to identify the eliciting allergen in these patients. This is done with the lymphocyte transformation test, but increasingly also by Elispot and with flow cytometric techniques. These analyses remain in the hands of specialised units that deal with these severely afflicted patients.

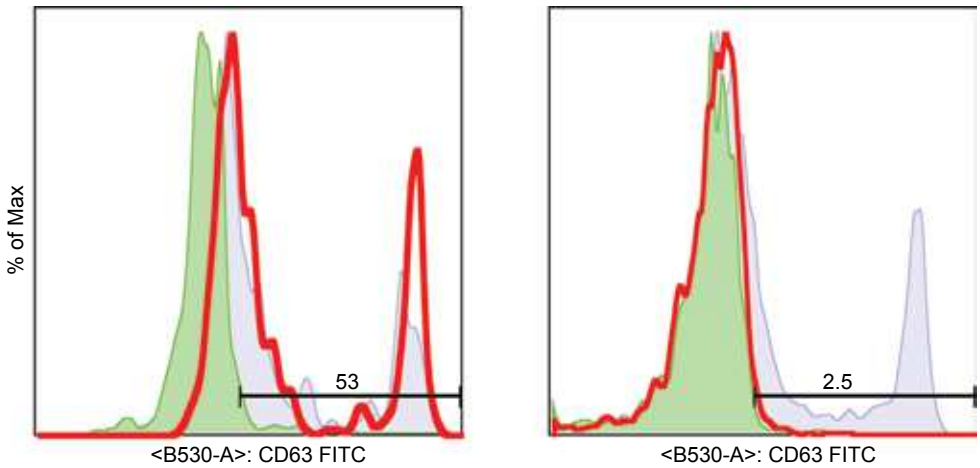

Figure 1 Basophil activation in clinical diagnosis of allergy to celery. Patient (left) with negative (green) and positive (blue) controls, and allergen response in red is reactive. A tolerant control person is shown on the right (unpublished).

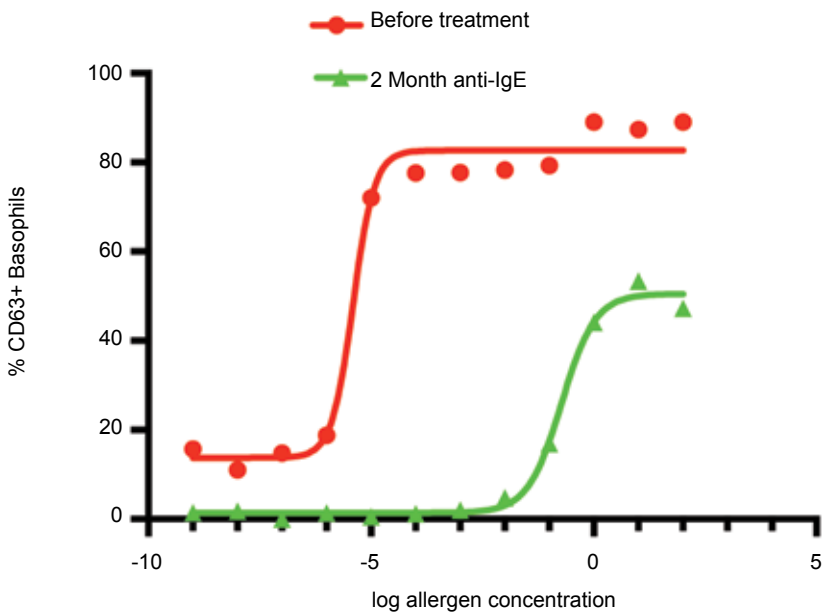

Figure 2 Anti-IgE treatment monitored with basophil sensitivity to allergen. Before treatment the patient was extremely sensitive (red) and after two months of treatment both sensitivity and reactivity had decreased (green). Rubak and Hoffmann, unpublished.

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4 BIOMARKERS FOR ALLERGY DIAGNOSIS AND TREATMENT

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KEY MESSAGES

- Novel biomarkers, as well as appropriate biomarker combinations are important to improve allergy diagnosis and treatment
- Classifying allergic diseases into several endotypes and using appropriate biomarkers to evaluate the molecular target for endotype will increase drug effectiveness
- Fractional exhaled nitric oxide is considered a surrogate biomarker for eosinophilic airway inflammation and for steroid responsiveness in asthma patients
- Periostin has emerged as a surrogate biomarker of type 2 inflammation and tissue remodeling in asthma

Biomarkers are used to diagnose diseases, estimate disease severity, or investigate underlying inflammation types, thus predicting the efficacy of therapeutics. For example, measuring a specific IgE or urinary leukotriene E4 is important for diagnosis of atopic status or aspirin-sensitive asthma, respectively. Discovering novel biomarkers, as well as finding appropriate combinations with existing biomarkers, is an important goal in allergy research aiming to improve diagnosis and treatment.

"Companion diagnostics", which can predict therapeutic efficacy, is now being widely recognized due the development of molecular targeted drugs against allergic diseases, particularly asthma. These drugs, mostly biologics, are expensive and are effective only for particular types of patients. It is now thought that asthma is not a single disease, but a "syndrome." Thus, it is important to classify asthma into several endotypes, based on their pathogenesis, and evaluate for which endotype, using the appropriate biomarkers each molecular targeted drug is effective using the appropriate biomarkers.

Although inhaled corticosteroids (ICS) provide beneficial effects for most asthma patients, 5-10% of patients are resistant or hypo-responsive to ICS. Any biomarker indicating the cause of the resistance to ICS would be useful. Moreover, biomarkers that can predict asthma relapse upon steroid reduction would be also valuable. Eosinophilc airway inflammation is at least one factor associated with steroid responsiveness. Fractional exhaled nitric oxide (FeNO) is considered a surrogate biomarker for eosinophilic airway inflammation and is regarded as a biomarker for steroid responsiveness (Figure 1). Although still controversial, the accumulated evidence has suggested that FeNO is useful for assessing control with ICS, predicting relapse upon ICS reduction, and estimating lung function.

Periostin, a downstream molecule of IL-4 and/or IL-13, has emerged as a surrogate biomarker of type 2 inflammation and tissue remodeling in bronchial asthma. It has been shown that serum periostin can predict the efficacy of anti-IL-13 antibody (lebrikizumab) and anti-IgE antibody (omalizumab), thus proving a prototype biomarker for the companion diagnostic of allergic diseases (Figure 2). Moreover, high serum periostin is linked to hypo-responsiveness for ICS, particularly in late-onset eosinophilic asthma (Figure 3). In addition to periostin, sputum eosinophils are useful for estimating the efficacy of anti-IL-5 antibody (mepolizumab).

FeNO	<25 ppb	25-50 ppb	50< ppb
Symptoms (+)	Consider alternative diagnosis	Uncontrolled	Uncontrolled
Symptoms (-)	Well controlled Consider taper or withdrawal	Well controlled	Risk of relapse upon ICS reduction

Figure 1 A treatment guideline for adult asthma patients based on existing symptoms and FeNO levels (Modified from Ref. 4)

Serum periostin	High	Low
Anti-IL-13 antibody (lebrikizumab)	Responsive	No responsive
Anti-IgE antibody (omalizumab)	Responsive	No responsive

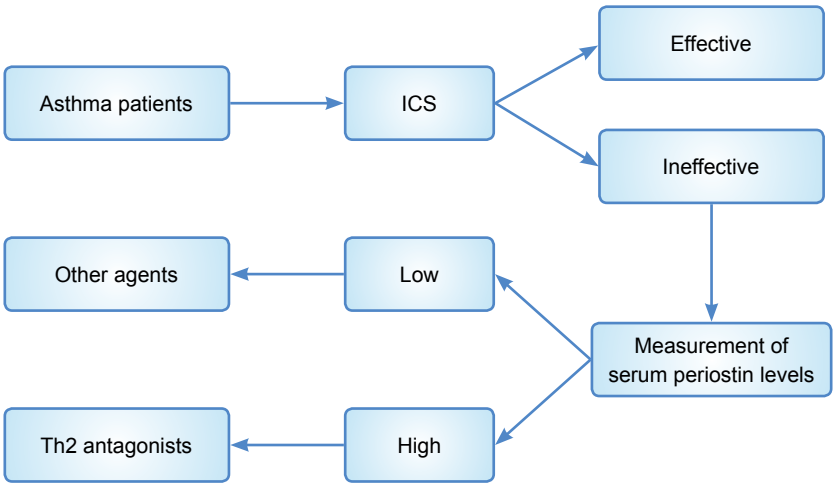

Figure 2 Serum periostin as a biomarker to select Th2 antagonists for asthma patients Upper panel: Responsiveness in asthma patients to Th2 antagonists depending on serum periostin is depicted. Patients showing high serum periostin are responsive to anti-IL-13 antibody (lebrikizumab) and anti-IgE antibody (omalizumab), whereas those showing low serum periostin are unresponsive to these agents. (Summarized from Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, Harris JM. Lebrikizumab treatment in adults with asthma. N Engl J Med 2011 365; 12, 1088-1098, Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy D F. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013 187; 804-811) Lower panel: An algorithm of treatment of asthma patients is shown. The first choice for asthma patients is ICS. If the patients are resistant to ICS, measurement of serum periostin is recommended. If serum periostin is high, Th2 antagonists are recommended; if low, other agents are recommended.

Genetic biomarkers, such as the filaggrin gene for skin barrier dysfunction or the glucocorticoid-induced transcript 1 gene for responsiveness to steroid therapy, represent another avenue to be explored in allergy research.

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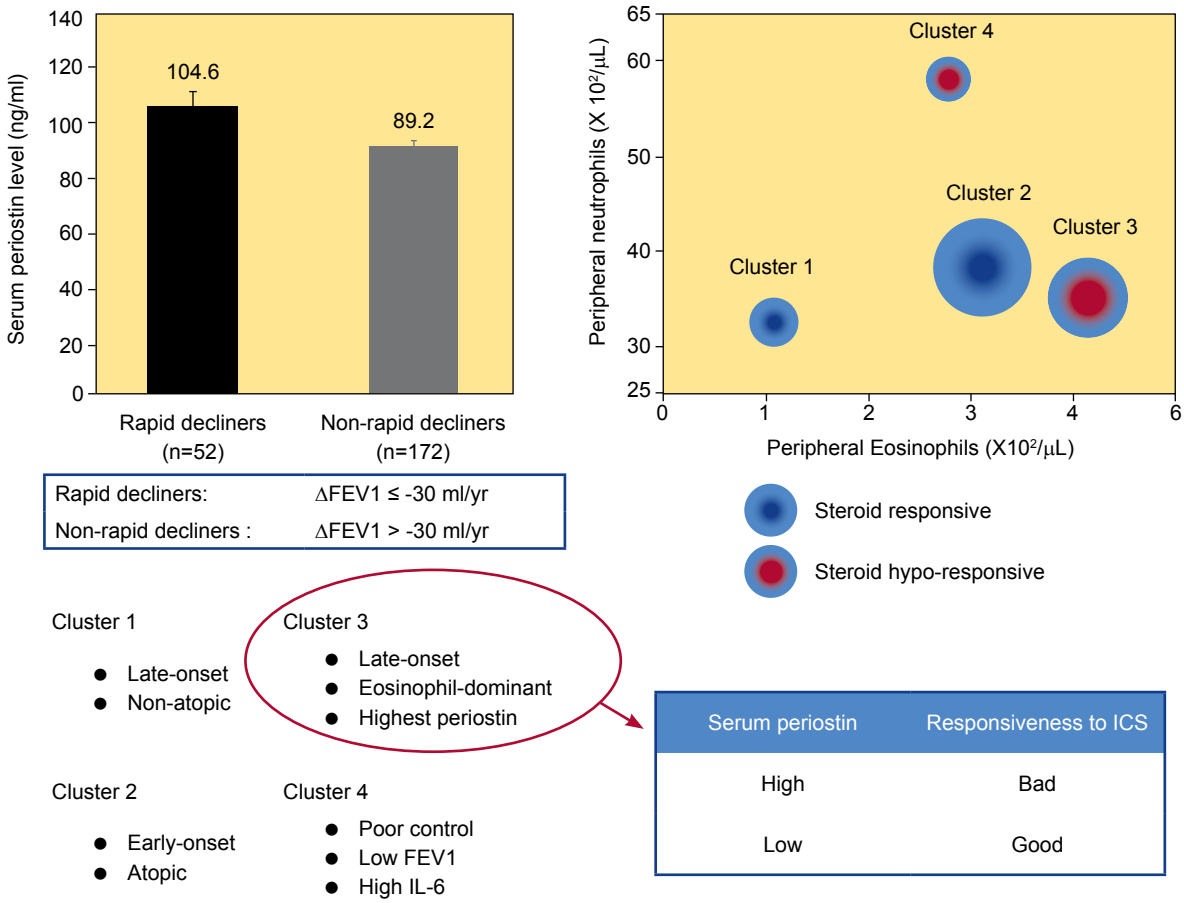

Figure 3 Serum periostin as a biomarker to predict responsiveness to ICS in asthma patients. Upper left panel: Serum periostin levels in rapid and non-rapid FEV1 decliners are depicted (8). Upper right panel: Clustering of asthma patients based on peripheral neutrophils and eosinophils is depicted. Lower left panel: Characteristics of each subtype are shown. Lower right panel: Correlation between serum periostin and responsiveness to ICS in cluster 3 is depicted. (*Reprinted from J Allergy Clin Immunol, 133/5, Nagasaki T, Matsumoto H, Kanemitsu Y et al. Integrating longitudinal information on pulmonary function and inflammation using asthma phenotypes, 1474-1477, Copyright 2014, with permission from Elsevier.*)

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Section D

MAJOR ALLERGIC DISEASES

* Allergic rhinitis
* Chronic rhinosinusitis and nasal polyposis
* Ocular allergy
* Pediatric Asthma
* Adult asthma
* Anaphylaxis
* Drug allergy
* Food allergy
* Atopic dermatitis
* Urticaria
* EAACI - GA²LEN - EDF - WAO Guideline on Urticaria
* Angioedema
* Allergic contact dermatitis
* Latex allergy
* Insect sting allergy
* Occupational allergy

1 ALLERGIC RHINITIS

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KEY MESSAGES

- Allergic rhinitis is a symptomatic IgE-driven inflammation of the nasal mucosa
- Allergen-specific IgE and eosinophilic inflammation are key features of allergic rhinitis
- The allergic reaction extends beyond the nasal cavity, with conjunctivitis and asthma often being associated with allergic rhinitis
- Treatment of allergic rhinitis aims at dampening the allergic immune response or inducing tolerance

Allergic rhinitis (AR) represents a **global health care problem** affecting 10 to 20% of the total population, making AR the most prevalent chronic non-communicable disease. Therefore, the **economic** impact of AR with significant direct and indirect costs should not be underestimated.

The **diagnosis** of AR is based on the history of the patient with minimally 2 nasal symptoms, with consistent findings at anterior rhinoscopy and positive skin prick test results or blood analysis for allergen-specific IgE. In AR, **CD4$^+$T** lymphocytes play a key role in the initiation and orchestration of the allergic immune response through the secretion of cytokines like IL-4, IL-5, IL-10 and IL-13 (Figure 1). IL-4 is a cardinal cytokine in driving the sensitization to allergens by inducing the IgE class switch in B lymphocytes. The cross-linking of allergens with allergen-specific IgE on the surface of mast cells leads to a rapid release of preformed mediators like histamine causing the symptoms of the **early nasal response**, i.e. sneezing, rhinorrhoea and nasal itching. Both histamine and tumor necrosis factor alpha (TNF-α), as well as newly generated lipid mediators like leukotriene C4 and prostaglandin D2, contribute to the influx of inflammatory cells like eosinophils, CD4$^+$ cells and basophils. The influx of these cells characterizes the **late allergic response** with mainly nasal obstruction as presenting symptom. Both allergen-specific IgE as well as eosinophilic nasal inflammation are features of AR and distinguish AR from **other forms of rhinitis** like infectious rhinitis, hormonal rhinitis, rhinitis medicamentosa, rhinitis in the elderly and non-allergic occupational rhinitis. Recently, regulatory T lymphocytes have been shown to be critical in the maintenance of immune responses. Naturally occurring CD4$^+$CD25$^+$ regulatory T cells and/or IL-10 producing Tr-1 cells suppress Th2 lymphocyte responses to allergens in health, whereas this inhibition is attenuated in allergic conditions. Successful **immunotherapy** for Th2 mediated allergic conditions is associated with the induction of IL-10 and TGF-β producing Tr-1 cells. Other forms of **medical treatment** aim at suppressing the allergic inflammatory cascade. The majority of AR is well controlled with guideline-based treatment. Several considerations need to be made in case of lack of control (Figure 2).

The allergic immune response involves a **nasal as well as systemic immune response**. The systemic nature of the allergic immune response with increased levels of IgE, IL-5 and blood eosinophilia has been recognized for several decades. In addition to nasal symp-

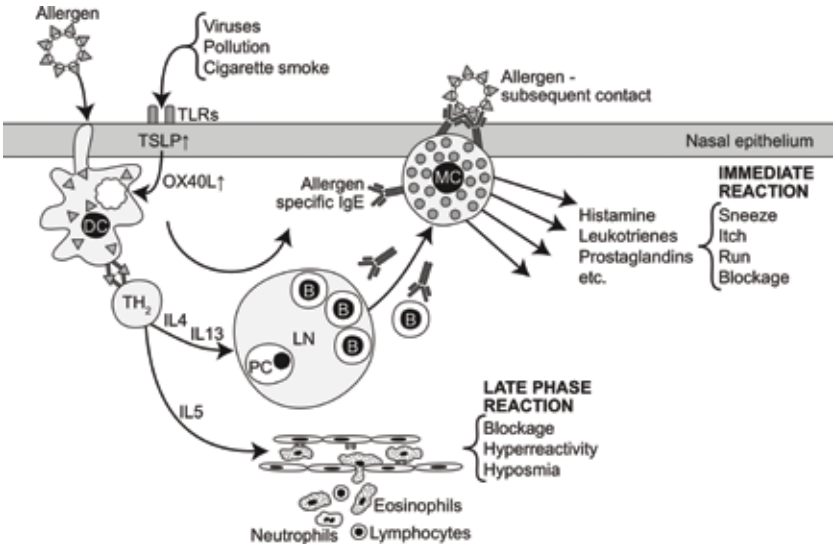

Figure 1 Mechanisms of immediate and late phase reaction in allergic rhinitis. (*Reprinted from The Lancet, 378, Greiner AN, Hellings PW, Rotiroti G, Scadding GK, Allergic rhinitis, 752-756, Copyright 2011, with permission from Elsevier.*)

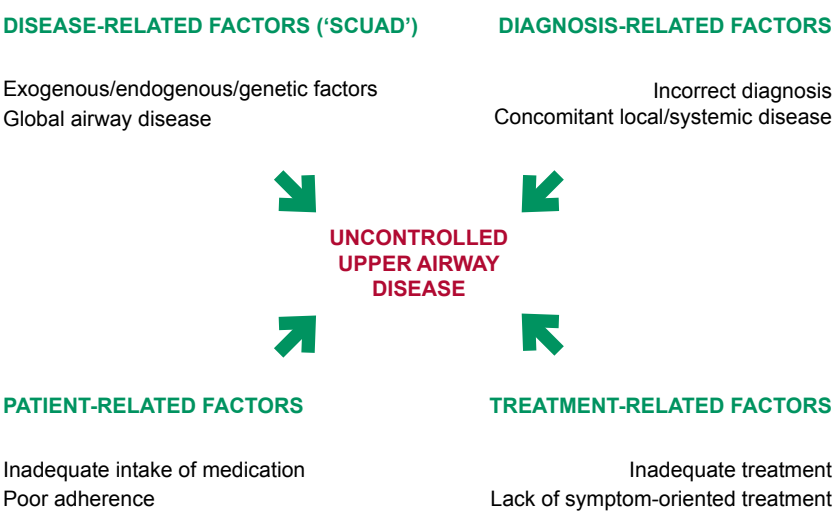

Figure 2 Considerations to be made in case of uncontrolled AR. (*Reproduced with permission from Hellings PW, Fokkens WJ, Akdis C et al. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? Allergy 2013;68:1-7, with permission from Willey Blackwell.*)

toms, inhalation of airborne allergens may give rise to **conjunctival symptoms** like itchy eyes, tearing, congestion of the conjunctival vessels, chemosis and periorbital oedema. AR may be a predisposing factor to develop disease in **adjacent structures** like the paranasal sinus cavities, middle ear, nasopharynx and larynx. From clinical studies, it is obvious that any neglect of an adequate diagnosis of sensitization to inhalant allergens may result in a suboptimal therapeutic approach of rhinosinusitis, tubal dysfunction and middle ear problems, laryngopharyngeal disorders and dysphonia. In view of the consideration of AR and **allergic asthma** (AA) being part of the airway allergy syndrome, we have nowadays good insight into the epidemiologic association between these two co-morbidities, diagnostic requirements for considering the problem of upper or lower airways as one entity, and therapeutic implications for optimal treatment of AR and AA. The immunologic mechanisms of the **naso-bronchial interaction** involve the systemic blood circulation as well as the naso-bronchial neural network.

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2 CHRONIC RHINOSINUSITIS AND NASAL POLYPOSIS

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CHRONIC RHINOSINUSITIS AND NASAL POLYPOSIS

Chronic rhinosinusitis (CRS) is one of the most common chronic medical conditions, with a significant impact on patient quality of life. CRS is broadly classified into two groups: CRS with nasal polyposis (CRSwNP) and CRS without NP (CRSsNP). CRS is defined as inflammation of the nose and the paranasal sinuses for ≥12 weeks, without complete resolution of symptoms. In CRSwNP, nasal polyps accompany the CRS inflammation. Polyps can be divided in eosinophilic and non-eosinophilic (NE). NE polyps demonstrate glandular hypertrophy and dense collagen deposition.

Recent data have demonstrated that CRS affects approximately 5–15% of the general population both in Europe and the USA. The prevalence of doctor-diagnosed CRS was 2-4%.

NPs were more frequent in men (2.2 to 1), in the elderly (5% at 60 years of age and older) and in asthmatics. In the USA, the prevalence of NP was found to be 4.2% with a higher prevalence (6.7%) in the asthmatic patients. The prevalence of CRS has been reported to be higher in smokers.

KEY MESSAGES

- Chronic rhinosinusitis (CRS) affects approximately 5–15% of the general population both in Europe and USA, with an increased incidence in smokers
- In the USA, the prevalence of NP was found to be 4.2% with a higher prevalence (6.7%) in the asthmatic patients
- Missed working days due to sinusitis reach 12.5 million, while reported restricted activity days were up to 58.7 million days in Europe
- National healthcare costs for CRS reach an estimated 8.6 billion dollar per year in the US

Mechanisms involved in CRS w/ wo NP involve both Th2-type and Th1/Th17 type inflammation, B cell activation and local production of high IgE levels, superantigens and biofilm formation (Table 2 and Figure 1). Several disease endotypes were proposed (Figure 2).

ECONOMIC COSTS OF CRSWNP

CRSwNP has a high impact on quality of life. Indirect costs are related to episodes of illness,

linked to missed workdays, disability claims, and absenteeism. Indirect costs account for 40% of the total costs of rhinosinusitis. Missed worked days due to sinusitis was 12.5 million and restricted activity days was 58.7 million days.

National health care costs in the US remain very high for CRS, at an estimated 8.6 billion dollar per year. In US the total cost of treating a patient with CRS was $2609 per year; in Europe the direct costs of a patient treated in a university hospital for severe chronic rhinosinusitis was $1861/year. Endoscopic sinus surgery is expensive, but causes a drop in costs for the 2 post-operative years. The ESS-procedure and the 45-day post procedure period count for $7,726 ($7,554 – $7,898).

Recommendations for CRSwNP treatment are shown in Figure 3.

TABLE 1

Diseases associated with CRSwNP	
Ciliary impairment	NPs are present in about 40% of patients with cystic fibrosis
Allergy	The prevalence with NP has been reported as varying from 10% to 64%.
Asthma	Reported by 26% of patients with CRSwNP
Aspirin sensitivity	36-96% patients have CRSwNP
Biofilms and S aureus	Correlated with severe forms of NPs

TABLE 2

Mechanisms involved in chronic rhinosinusitis
Eosinophil levels and Th2 cytokine skewing are most closely associated with Western CRSwNP
Asian polyps are less eosinophilic than Western CRSwNP, exhibiting a Th1/17 cytokine skewing
CRSwNP exhibits oedema, low TGF-β levels and low T regulatory cells activity.
Increase in T lymphocytes numbers and activated T-lymphocytes, CD4+/ CD8+ T cells, and eosinophils
Elevations of tissue B cells, plasma cells and immunoglobulins (high local IgE levels) are associated with CRSwNP
Approximately 50% of CRSwNP patients demonstrate B and T cells responses in the tissue consistent with prior local staphylococcal superantigen exposure
Biofilms and/or intracellular residence of bacteria may increase resistance to standard therapy
Allergic fungal rhinosinusitis is associated in 14% of CRSwNP
Levels of Vitamin D3, an immunoregulatory molecule were low in CRSwNP suggesting a potential role for replacement therapy

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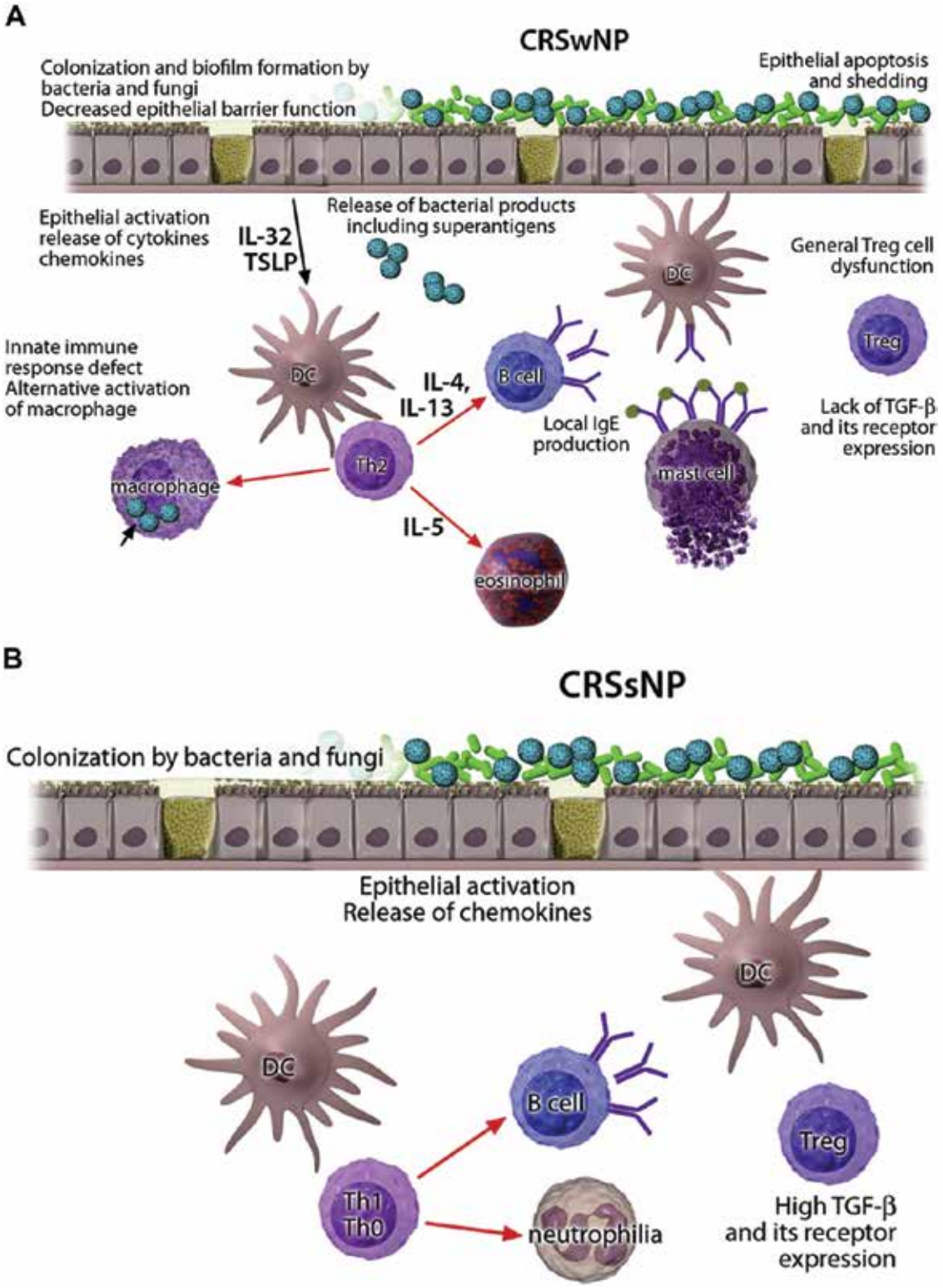

Figure 1 Mechanisms behind chronic rhinosinusitis. (*Reprinted from J Allergy Clin Immunol, 131/6, Nagasaki T, Akdis CA, Bachert C, Cingi C et al. Endotypes and phenotypes of chronic rhinosinusitis, 1479-1490, Copyright 2013, with permission from Elsevier.*)

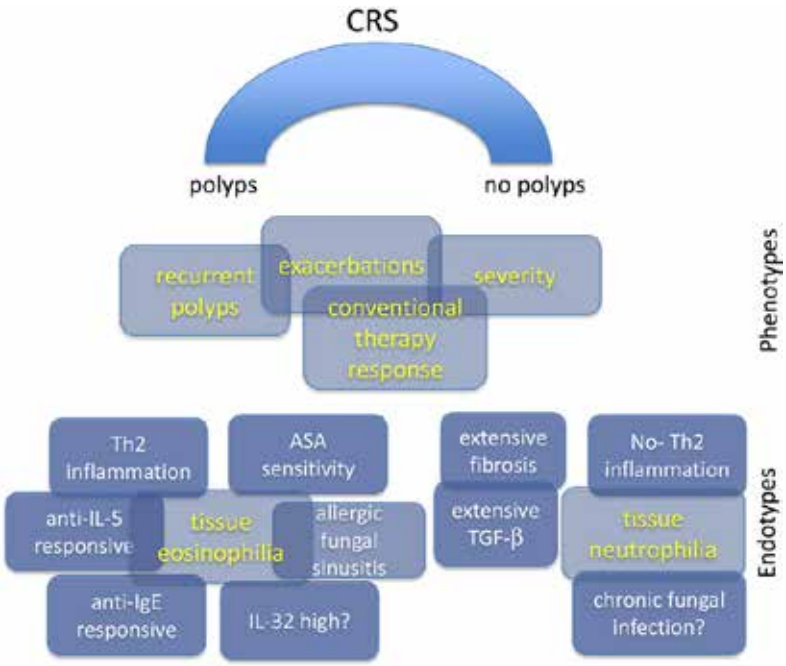

Figure 2 Proposed disease phenotypes and endotypes in CRS. (*Reprinted from J Allergy Clin Immunol, 131/6, Nagasaki T, Akdis CA, Bachert C, Cingi C et al. Endotypes and phenotypes of chronic rhinosinusitis, 1479-1490, Copyright 2013, with permission from Elsevier.*)

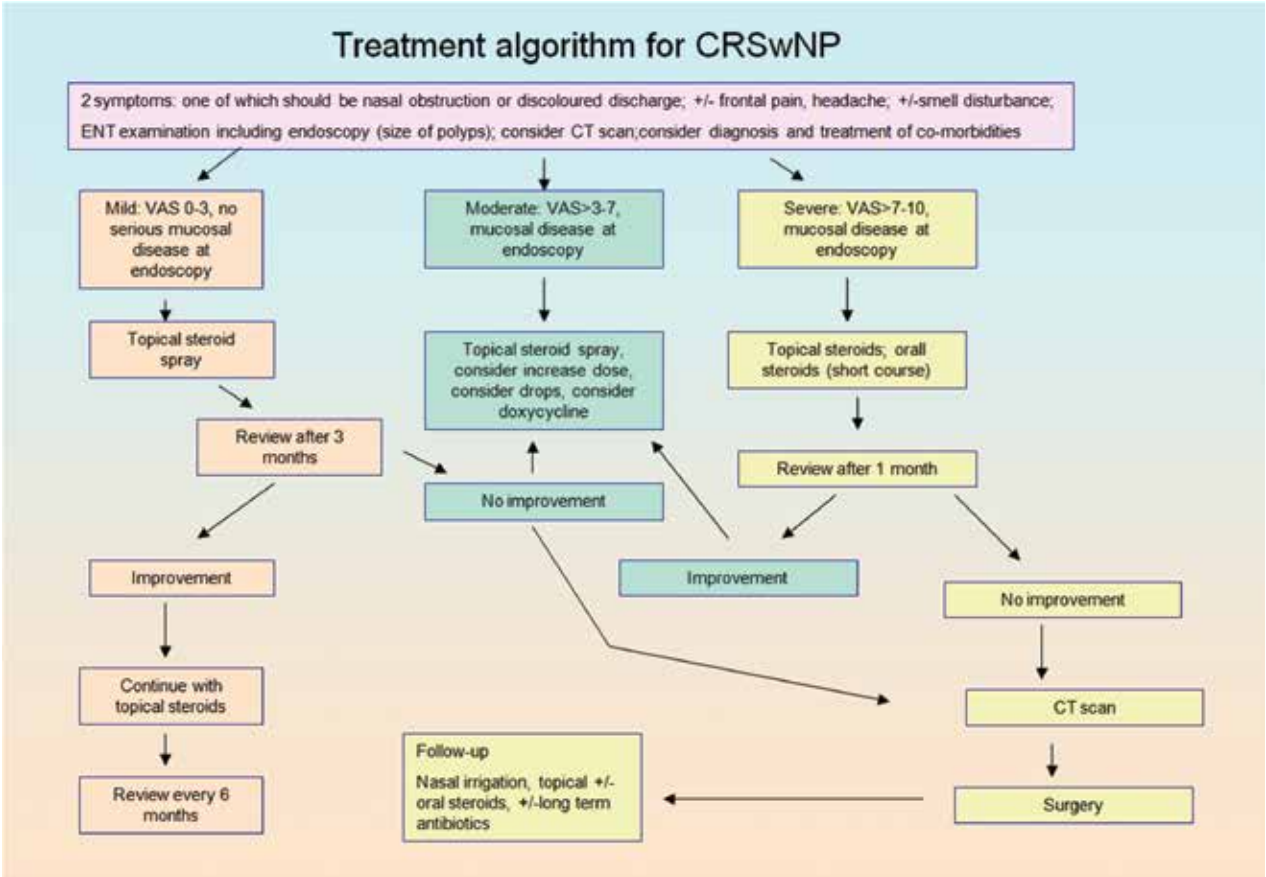

Figure 3 Treatment evidence and recommendations for CRSwNP. (*Adapted from Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl. 2011; 1-298.*)

3 OCULAR ALLERGY

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KEY MESSAGES

- Allergic conjunctivitis (AC) is the commonest of all allergic disorders affecting approximately 25% of the population; it most commonly occurs with allergic rhinitis; seasonal and perennial AC, while not life-threatening, have a significant impact on quality of life
- Dry eye and AC frequently co exist and both require optimal management
- AC benefits from use of intranasal corticosteroids as well as specific topical ocular therapy
- The complex disorders, atopic keratoconjunctivitis and vernal keratoconjunctivitis are sight threatening, may require use of topical corticosteroids and require co- management with an ophthalmologist
- Potent, well-tolerated topical mast cell stabilisers have greatly improved management of ocular allergy; there is no role for topical corticosteroids in AC; newer immunosuppressive agents may be beneficial in sight- threatening forms of AC

Allergic conjunctivitis (AC) refers to a broad group of disorders involving inflammation of the conjunctiva and presents in a number of forms. It is the most common ocular allergic disorder affecting approximately 25% of the population and is responsible for presentation to a number of doctors including general practitioners, allergists and ophthalmologists. The characteristic s of AC include ocular itch, tearing, redness, chemosis and lid oedema (Figure 1). Itch is considered a hallmark symptom but may also be experienced in those with dry eye. Signs are usually more dramatic and obvious in those with SAC compared to those with PAC.

Seasonal and perennial AC (SAC and PAC) are the most common forms and most frequently occur with nasal allergy. They are caused by a classic type 1 hypersensitivity reaction to common aeroallergens. SAC, accounting for approximately 80% of all ocular allergy cases, usually has a more dramatic appearance and is more problematic than PAC. Triggers are those for seasonal allergic rhinitis, typically, pollen from trees, grasses and weeds. PAC is similar to SAC, but is experienced year round. It is triggered by chronic exposure to aeroallergens such as house dust mite, animal dander and mould. In general, SAC and PAC are self limiting, depending on allergen exposure.

Other forms of ocular allergy, namely vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) are potentially sight-threatening disorders. They have a much more complex immunopathophysiology. VKC is uncommon, occurring in children and teenagers with a male predominance of 2:1. There is seasonal variation in severity although the condition is not directly caused by aeroallergen exposure and is more severe and prevalent in hot, dry climates. It usually runs a course spanning 2-10 years and is always eventually outgrown. Intense itch, marked photophobia and a ropey discharge are characteristic symptoms while physical examination most often reveals upper lid swelling with cobblestoning of the superior palpebral conjunctiva, when the lid is everted. Other signs include Trantas dots (composed of eosinophils and cellular debris; seen around the limbus), and in severe cases, corneal in-

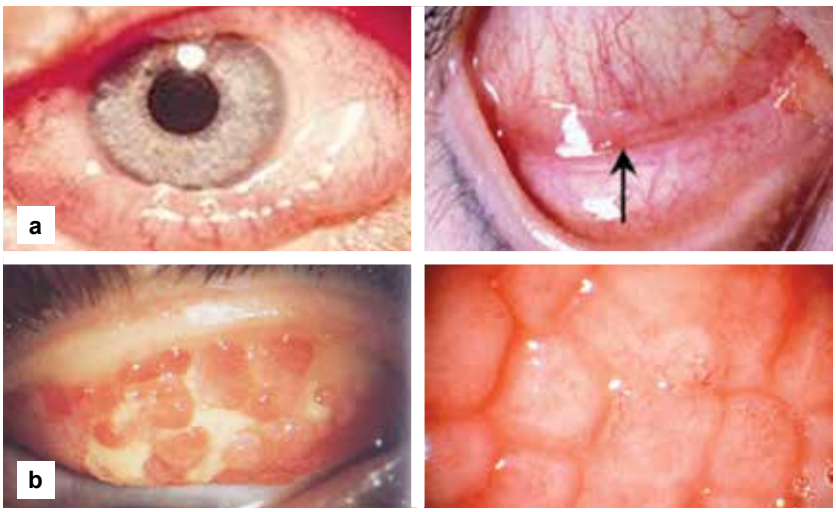

Figure 1 a - tearing, redness, chemosis and lid oedema in allergic conjunctivitis; b - cobblestoning of the superior palpebral conjunctiva in atopic and vernal keratoconjunctivitis.

volvement may occur, ranging from punctuate keratitis to shield ulcer formation which can be sight threatening. AKC is the chronic, bilateral, severe conjunctivitis associated with atopic dermatitis. It develops in approximately 25% of the adult atopic dermatitis population with skin signs preceding ocular inflammation and eyelid eczema a common accompaniment. Symptoms may be debilitating; subconjunctival scarring and distortion of lid margins may occur; chronic conjunctival inflammation and tear film disturbance may lead to ulceration, scarring and vision loss. Of all AKC patients, about 5% develop cataract and are at risk of other complications such as keratoconus, retinal detachment and herpetic ocular infection.

Giant papillary cell conjunctivitis is a condition not seen as frequently these days. It is caused by chronic exposure to a foreign body and was most commonly seen with long term contact lens use but with modern daily lenses, this is much less frequently seen. It may be seen in those with ocular prostheses and ocular sutures. Dry eye syndrome results from decreased tear production or disruption to the tear film stability. It can be confused with allergy and can commonly co-exist with AC. It is worsened by the use of oral antihistamines. Regular use of lubricants is a useful additional therapeutic option in these patients as they assist in removal of allergen and relieve symptoms simultaneously.

Management strategies for all forms of AC begin with allergen identification, removal or minimisation, then trials of non pharmacological therapy such as eye irrigation and lubrication and pharmacological therapy. Treating the nasal component of allergic rhinoconjunctivitis can bring significant relief from the ocular symptoms but several specific ocular allergy treatments are also available. In general, topical antihistamine preparations are much more effective than oral antihistamines which can exacerbate the dry eye component if taken regularly. A number of mast cell stabilising agents are available for those who experience frequent and distressing symptoms; these must be commenced 1-2 weeks before the anticipated onset of the allergy season to give maximum relief. They are often used in combination with symptomatic topical antihistamine therapy. Medications with multiple actions (mast cell stabilising and antihistamines) have become mainstay treatment for patients with more troublesome symptoms.

Topical corticosteroids are an important component of management of VKC and AKC, but their use must be monitored carefully by an ophthalmologist. Topical cyclosporin (Restasis) may be useful in those with a T cell driven chronic inflammation such as VKC and AKC, where it can be steroid sparing.

Ocular allergy is most commonly managed by the general practitioner, but a patient, who is non-responsive to standard therapy, or who has one of the complex, potentially sight-threatening disorders, or who requires topical corticosteroids needs to be referred for specialist management.

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4 PEDIATRIC ASTHMA

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KEY MESSAGES

- Over the last 20 years, more emphasis has been placed on recognizing the burden of asthma in children, and steps have been taken to recognize the disease and to intervene earlier
- Standardized outcome measures for treatment effects are not clear, especially in young children
- The younger the child, the more limited the information available on efficacy and safety of medication. As children get older, the principles of treatment closely reflect those used in older children and adults
- Current research in pediatric asthma is directed at methods to eliminate asthma exacerbations and to alter the natural history of asthma

WHAT IS ASTHMA?

In the current update of the Global Initiative for Asthma, asthma is described as a heterogeneous disease, usually characterized by airway inflammation, and defined by the presence of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. It is a chronic respiratory disease that can affect 1 to 18% of the population with considerable variability among countries (Figure 1). The variation of symptoms over time is triggered by factors such as exercise, allergen exposure, weather, or viral respiratory infections. Symptoms and airflow limitation may resolve spontaneously or in response to medication, and may sometimes be absent for weeks or months at a time. Patients can experience episodic flare-ups (exacerbations) of asthma that may be life-threatening and carry a significant burden to patients and the community.

While there are no confirmatory diagnostic tests, asthma can present in early childhood as respiratory tract illnesses. With increasing frequency of these illnesses, respiratory distress appearing between illnesses, and the development of allergy, the diagnosis becomes apparent. Symptoms are temporarily relieved with short-acting bronchodilator therapy. An increase in symptoms often triggers the initiation of long-term controller therapy, especially inhaled corticosteroids.

Over the last 20 years, more emphasis has been placed on recognizing the burden of asthma, especially in children, and steps have been taken to recognize the disease and to intervene earlier. However, standardized outcome measures for treatment effects are not clear, especially in young children. The current state of asthma management is summarized in the Global Initiative for Asthma Strategy Report.

WHERE DO WE GO FROM HERE?

Clinicians are not satisfied with the available tools to diagnose and monitor asthma. Our current treatment has evolved over time to emphasize long-term controller therapy to prevent symptoms (Figure 2). However, the younger the child, the more limited the information available on efficacy and safety of medication. As children get older, the principles of treatment closely reflect those used in older children and adults.

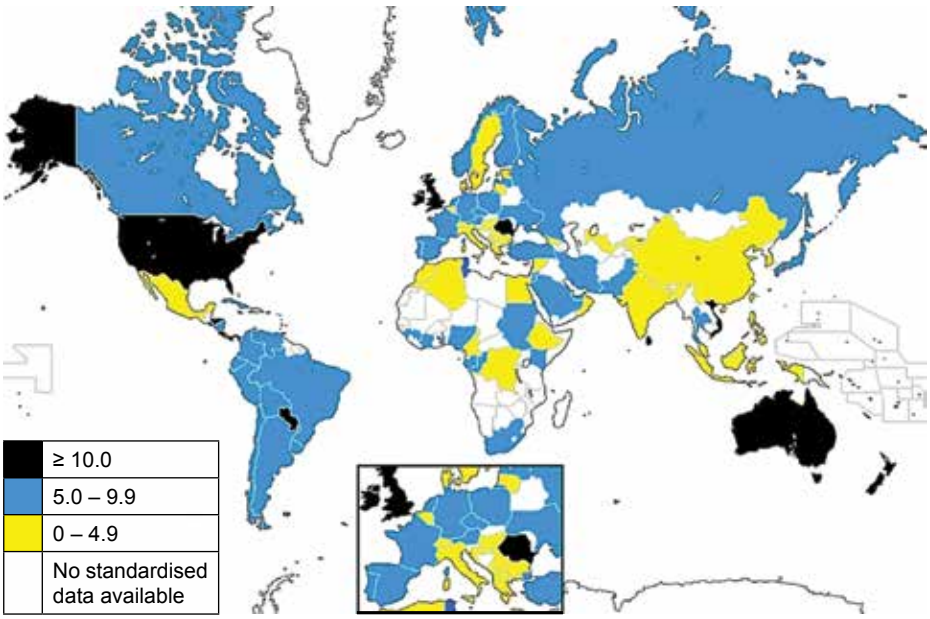

Figure 1 Data are "provide" by Dr. Richard Beasley and based on ISAAC Phase III (Lai CKW et al. Thorax 2009; 64: 476-83). Where no data are available from ISAAC Phase III, prevalence figures have been taken from the Global Burden of Asthma Report (Masoli M et al. Allergy 2004; 59: 469-78). The prevalence of current asthma in the 13-14 year age group is estimated at 50% of the prevalence of self-reporting wheezing in the previous 12 months. (*From the Global Strategy for Asthma Management and Prevention (Online Appendix), revised 2014, © Global Initiative for Asthma (GINA) all rights reserved. Available from http://www.ginasthma.org.*)

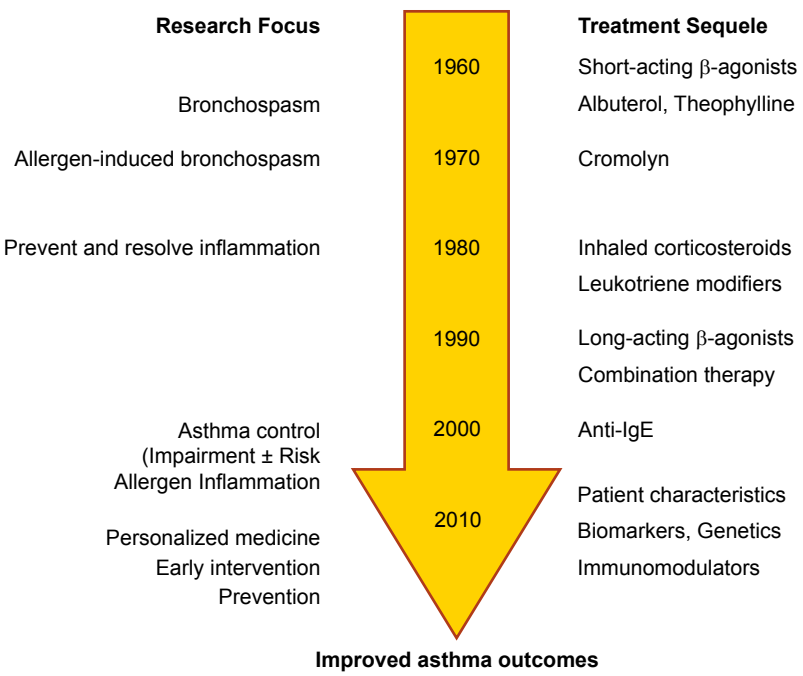

Figure 2 Advances in asthma treatment based on an effort to improve asthma outcomes.

Current research in pediatric asthma is directed at methods to eliminate asthma exacerbations and to alter the natural history of asthma. Efforts are being made to understand the factors contributing to asthma exacerbations and progression of the disease. The future is bright for advancing asthma care to recognize the disease early, intervene more effectively, and further reduce asthma morbidity and mortality.

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5 ADULT ASTHMA

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KEY MESSAGES

- Asthma involves the entire respiratory tract from the upper airways to the peripheral small airways
- Steroid refractory airway inflammation and remodeling is a common phenomenon in adult asthma
- Insufficient asthma control by standard inhaled corticosteroid therapy is either due to uncontrolled small airway inflammation or uncontrolled co-morbidity
- Future sthma therapy should address the systemic component of the disease and the aim should be to, not only control, but to modify the course of the disease

INTRODUCTION

Asthma is a global problem affecting around 300 miljon individuals around the world and as it mostly involves people in working ages, the socioeconomic burden is high. The common view of asthma have changed considerably during the last 50 years. From initially being regarded as primarily a bronchospastic disorder, the inflammatory part of the disease and lately the systemic inflammatory part has been increasingly recognized. The new view of asthma as a primarily a systemic inflammatory disorder, will call for new management and treatment strategies, closely linked to Allergology and Clinical Immunology.

FROM RELEASE OF BRONCHOSPASM TO CONTROLLING AIRWAY INFLAMMATION

During the last decade there has been several paradigm shifts in the understanding of the disease mechanisms in adult asthma. In the 60th -70th much focus was on the smooth muscle component and the systemic and inhaled bronchodilators were used both as maintenance therapy and during acute attacks. From late 70th a paradigm shift occurred from bronchodilation to anti-inflammatory treatment mainly with inhaled corticosteroids. Asthma was regarded as a central airway, eosinophilic disorder and it was believed that proper anti-inflammatory treatment with inhaled corticosteroids (ICS) can achieve asthma control, and in some cases, even could cure the disease. However, it soon became clear that ICS treatment only controlled parts of the disease with a rapid relapse as soon as the ICS treatment was stopped. Even though corticosteroids cover a wide range of the asthmatic inflammation, there are other steroid refractory mechanisms that in the long run induces tissue changes, i.e. airway remodelling, resulting in persistent airway hyper responsiveness and an accelerated lung function decline. Chronic asthmatic inflammation and tissue remodeling, thus represents one of the major future challenges in asthma management.

THE IMPORTANCE OF SMALL AIRWAYS IN ASTHMA

It is a well-recognized fact that a large fraction of patients treated with ICS do not achieve acceptable clinical control, even when bad adherence is corrected for. One probable explanation is that ICS do not cover all aspects of the asthmatic inflammation (different inflammatory endotypes). It has also been shown that these patients have an increased, partially steroid resistant inflammation in the peripheral airways. The pe-

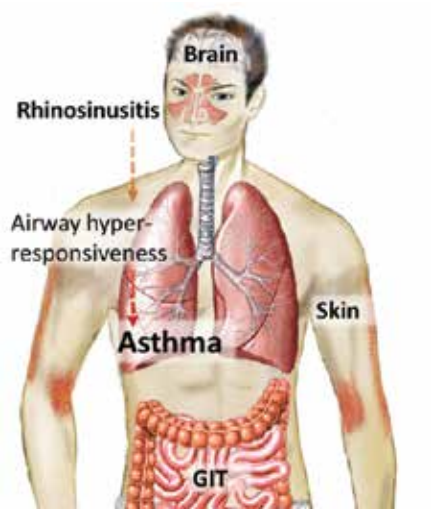

Figure 1 The new view of asthma as a systemic inflammatory disorder with a close link between the upper and the lower airways. The majority of patients with asthma have concomitant rhinosinusitis. Many patients with rhinitis/rhinosinusitis have airway hyperresponsiveness, while development of clinical asthma is associated with an extended involvement of the peripheral "small airways". The respiratory system is also under the influence by co-morbid conditions related to the gastrointestinal tract (food sensitization, bowel inflammation), the Skin (eczema, barrier dysfunction) as well as the nervous system (neuroimmunologic network, cognitive dysfunction).

ripheral small airways, usually referred to as the "silent zone", provides less than 10 % of airway resistance but more than 90 % of the total volume. This may explain lung function measured as PEF or FEV relates poorly to important asthma outcomes, such as symptoms, exacerbations and quality of life. In the clinical context, small airways are not that silent. Important features of the disease such as nocturnal or exercise induced symptoms, risk for asthma exacerbations are all related to uncontrolled inflammation in the small airways.

FROM A LUNG DISEASE TO A SYSTEMIC INFLAMMATORY DISORDER

The traditional view of asthma has been organ centered, focusing on asthma as a pure lung disorder. However, in the real life setting, most of the patients with asthma have one or more co-morbidities interfering with the disease. More than 80% of patients with asthma have concomitant rhinitis or rhinosinusitis and this link becomes stronger by disease severity. Thus, with more severe uncontrolled disease, concomitant rhinitis/rhinosinusitis is almost always present. Unfortunately, this obvious fact has been ignored by the pharmaceutical companies developing asthma drugs, excluding the most common asthma phenotype, i.e. the *asthma-rhinitis* patient from clinical asthma trials.

Not only the upper airways have a great impact on the asthma control. It is well known that food allergen sensitization increases the risk for asthma development later on in life. Recent data also suggests a close link between skin barrier dysfunction, dermatitis and inflammation in the airways. Thus, not only the lungs, but also a reduced skin barrier may be an important entrance for allergic sensitization also to airborne allergens.

A third important link with systemic inflammation and asthma is the neuroimmunologic network (Figure 1). Anxiety and depression are more prevalent among patients with asthma and allergy. Moreover, the neuroendocrine response to biological stress affects several somatic functions including the airways and this will probably be a very important research area in the near future.

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Global Atlas of Asthma

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

Asthma from epidemiology, risk factors and mechanisms to phenotypes and management

Diseases associated with asthma

Major current problems in asthma

Prevention and control of asthma

6 ANAPHYLAXIS

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KEY MESSAGES

- Anaphylaxis is diagnosed based on validated clinical criteria. It is commonly IgE-mediated, but can also occur through IgE-independent immune mechanisms or direct mast cell stimulation.
- Vulnerable patients with anaphylaxis include infants, adolescents, pregnant women, the elderly, patients with asthma, cardiovascular disease, mast cell activation disorders, and those concurrently taking certain medications. Amplifying co-factors include exercise, infection, and emotional stress.
- Initial treatment focuses on prompt epinephrine (adrenaline) intramuscular injection in the mid-outer thigh, calling for help, positioning the patient supine, providing supplemental oxygen and intravenous fluids, and vigilant monitoring.
- Post-discharge management includes preparing the patient to treat recurrences in the community, and preventing recurrences by confirming the anaphylaxis trigger(s), and initiating allergen avoidance and immune modulation.

Anaphylaxis is a serious allergic or hypersensitivity reaction that can cause death. It is rapid in onset (minutes to a few hours) and typically involves multiple body systems. The lifetime prevalence of anaphylaxis from all triggers is at least 1%. Patient factors and co-factors that affect anaphylaxis are similar worldwide (Figure 1). The importance of different anaphylaxis triggers varies with age and geography. Anaphylaxis commonly occurs through an IgE-dependent immunologic mechanism triggered by foods, stinging insect venoms, medications or latex. It can also be induced by other immunologic mechanisms or by direct mast cell stimulation. In idiopathic anaphylaxis, the possibility of a novel trigger or a mast cell activation disorder should be considered (Figure 2).

Clinical criteria for the diagnosis of anaphylaxis have been validated for use in medical settings and epidemiologic studies and have high sensitivity, good specificity, and a high negative predictive value. Skin and mucous membrane symptoms and signs such as itching, flushing, hives, and angioedema are present in 80-90% of episodes. Respiratory, gastrointestinal, and cardiovascular symptoms are also common; however, shock is not necessarily present, even in severe or fatal anaphylaxis (Figure 3).

Initial management involves having a protocol, assessing the patient, then promptly and simultaneously calling for help, injecting epinephrine (adrenaline) intramuscularly in the mid-outer thigh and positioning the patient supine or in a position of comfort. Supplemental oxygen, intravenous fluid resuscitation and cardiopulmonary resuscitation should be provided. Heart rate and function, blood pressure, and oxygenation should be monitored, if possible, H_1-antihistamines, H_2-antihistamines, glucocorticoids, and beta-2 adrenergic agonists should not be administered before epinephrine treatment, or as monotherapy (Figure 4). Patients with anaphylaxis refractory to epinephrine, supplemental oxygen, and intravenous fluid resuscitation need intensive care treatment with ventilatory and inotropic support.

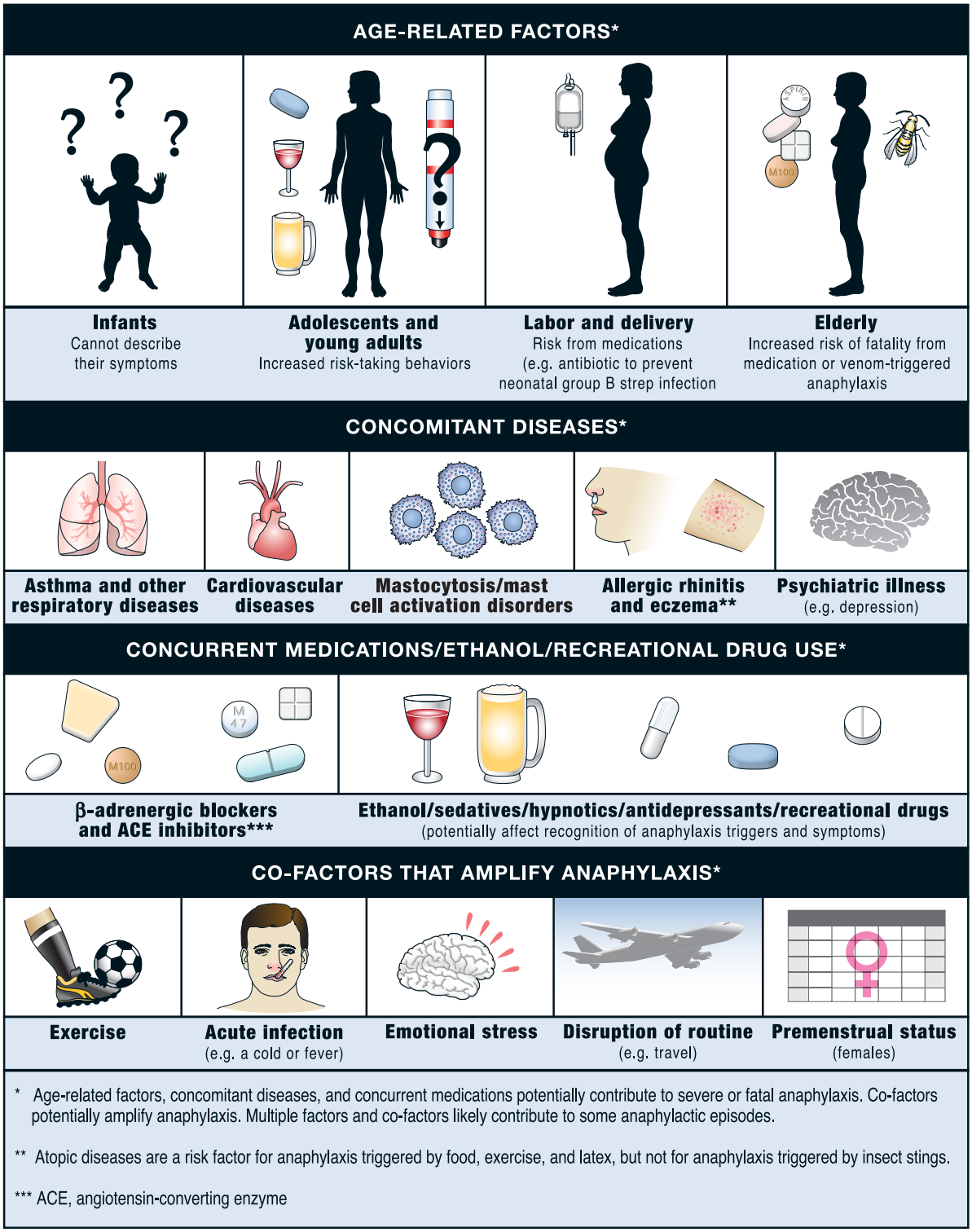

Figure 1 Age-related factors, concomitant diseases, concurrent medications, and amplifying co-factors in anaphylaxis. Multiple factors and cofactors likely contribute to some anaphylactic episodes. (*Reprinted from J Allergy Clin Immunol, 127/3, Simons FER, Ardusso LRF, Bilo MB, et al. World Allergy Organization anaphylaxis guidelines: summary, 587-593.e1-e22, Copyright 2011, with permission from Elsevier.*)

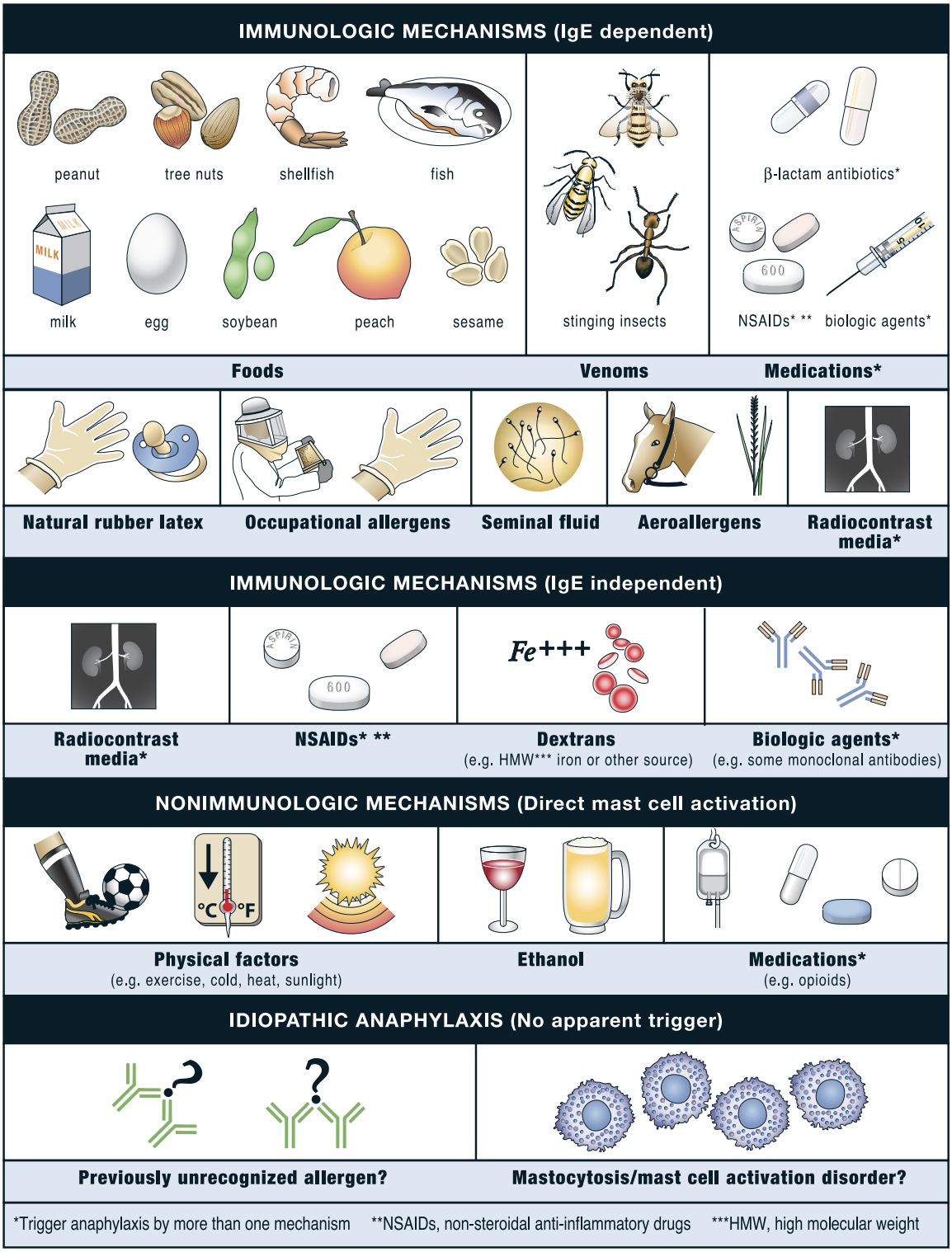

Figure 2 Anaphylaxis mechanisms and triggers. Anaphylaxis is commonly triggered by an allergen through an IgE-dependent mechanism; however, it can also be triggered through other immunologic mechanisms or direct mast cell stimulation. (*Reprinted from J Allergy Clin Immunol, 127/3, Simons FER, Ardusso LRF, Bilo MB, et al. World Allergy Organization anaphylaxis guidelines: summary, 587-593 .e1-e22, Copyright 2011, with permission from Elsevier.*)

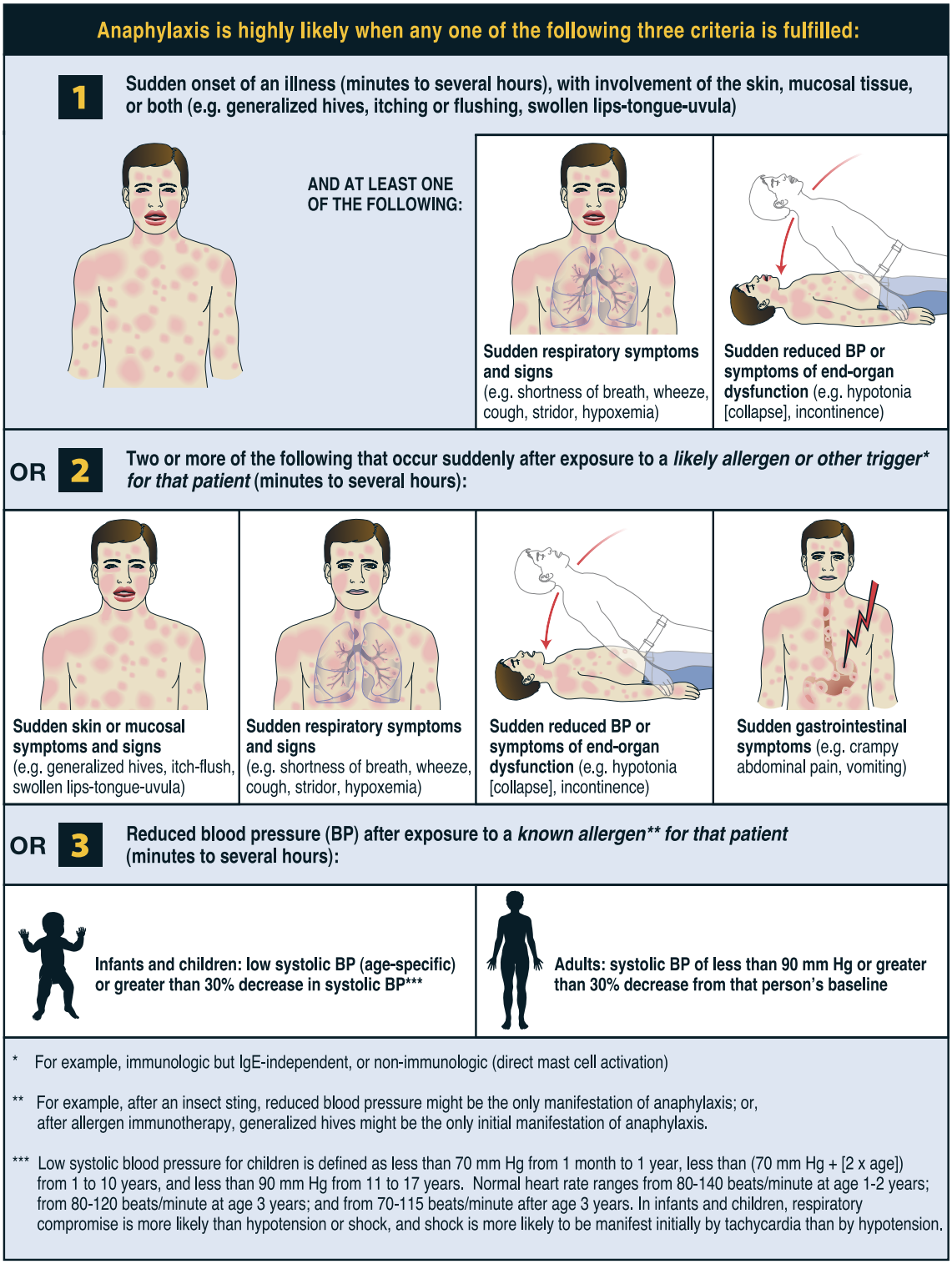

Figure 3 Clinical criteria for the diagnosis of anaphylaxis. These criteria were developed as an instrument to aid in recognition of anaphylaxis in patients with a sudden onset of characteristic symptoms and signs. They have been validated for use in clinical and epidemiologic studies. (*Reprinted from J Allergy Clin Immunol, 127/3, Simons FER, Ardusso LRF, Bilo MB, et al. World Allergy Organization anaphylaxis guidelines: summary, 587-593 .e1-e22, Copyright 2011, with permission from Elsevier.*)

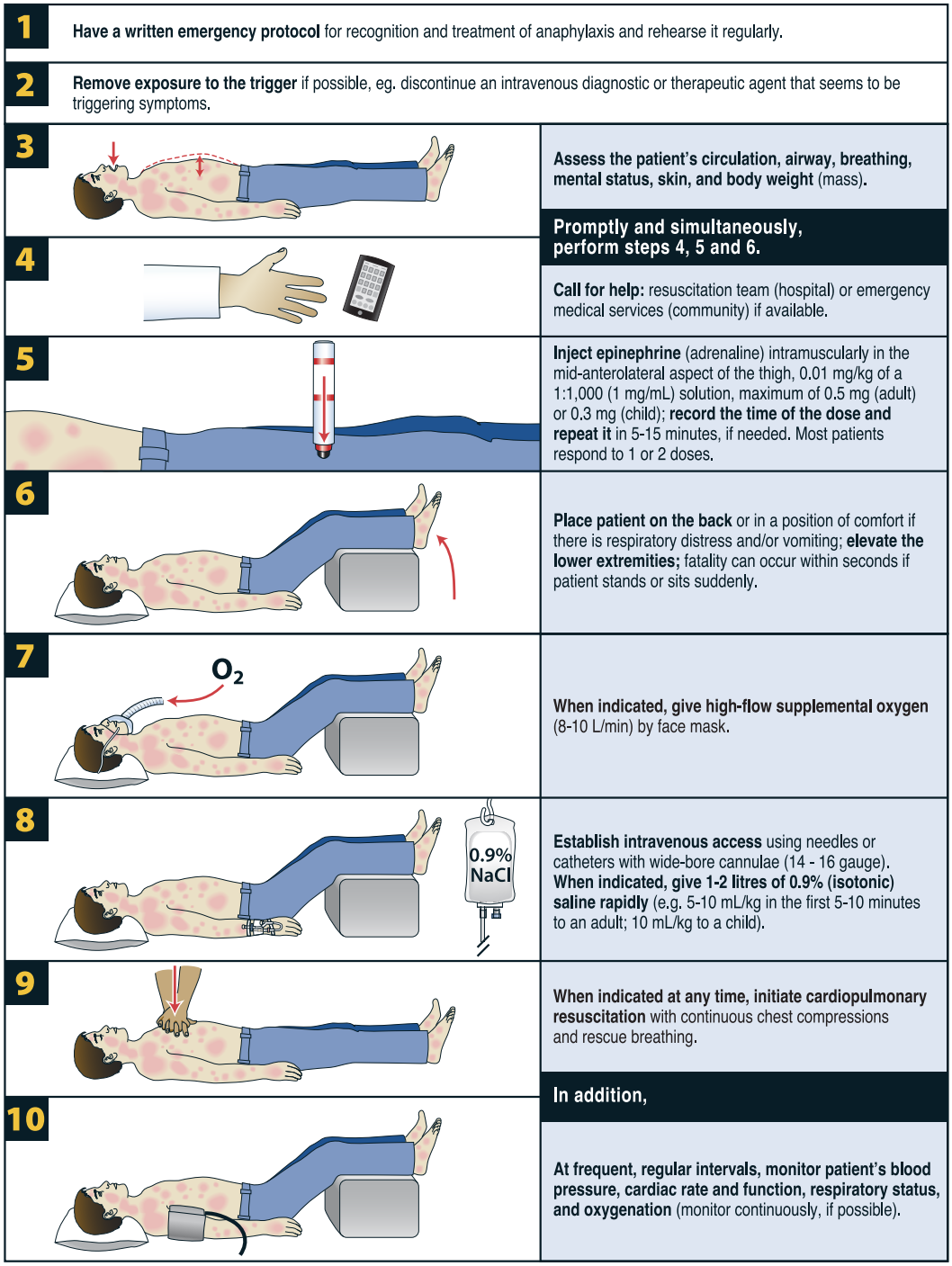

Figure 4 Initial management of anaphylaxis. Preparedness is critically important. Treatment should be initiated as soon as anaphylaxis is recognized, as death can occur within minutes. Before initiating rescue breaths, cardiopulmonary resuscitation should begin with chest compressions (rate 100-120/minute and depth of 5-6 cm in adults; rate of ≥ 100 compressions/minute and depth of 5 cm in children [4 cm in infants]). (*Reprinted from J Allergy Clin Immunol, 127/3, Simons FER, Ardusso LRF, Bilo MB, et al. World Allergy Organization anaphylaxis guidelines: summary, 587-593 .e1-e22, Copyright 2011, with permission from Elsevier Reprinted from J Allergy Clin Immunol, 117/2, Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium, 391-397 Copyright 2006, with permission from Elsevier.*)

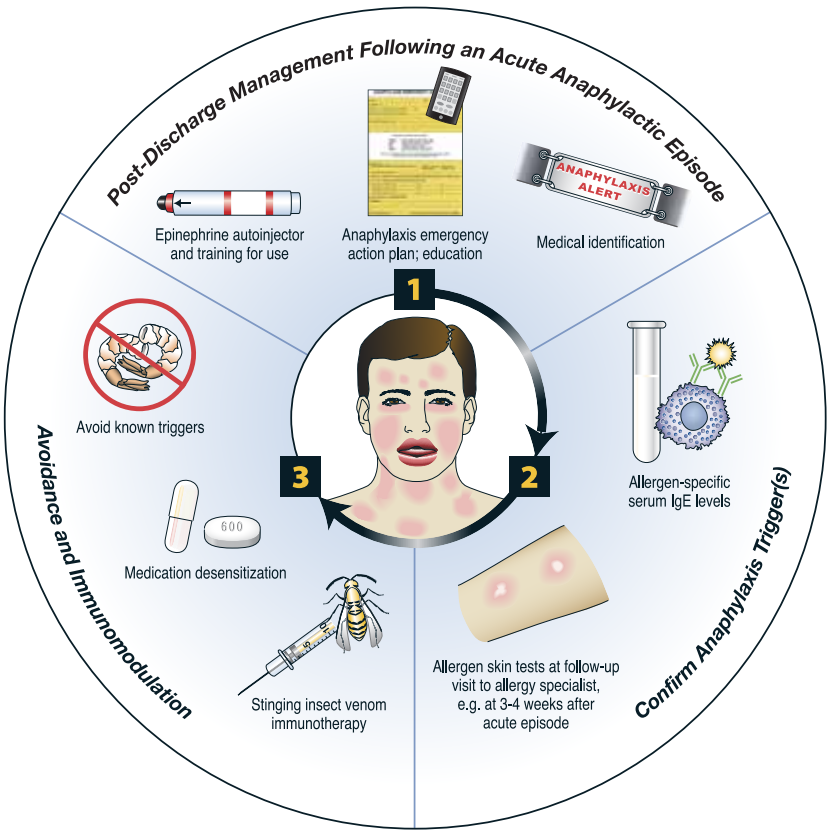

Figure 5 Post-discharge management. Panel 1: post-discharge management after treatment of anaphylaxis in a healthcare setting. Panel 2: anaphylaxis triggers suggested by the history are confirmed by skin tests and measurement of allergen-specific IgE levels. Panel 3: long-term management involves avoidance of confirmed trigger(s) and relevant immune modulation. (*Reprinted from J Allergy Clin Immunol, 127/3, Simons FER, Ardusso LRF, Bilo MB, et al. World Allergy Organization anaphylaxis guidelines: summary, 587-593 .e1-e22, Copyright 2011, with permission from Elsevier.*). Figures 1-5 prepared by J. Schaffer.

After treatment of an anaphylactic episode, a patient should be prepared to self-manage recurrences in the community by consistently carrying one or more epinephrine auto-injectors and injecting epinephrine promptly, when anaphylaxis occurs; also by developing and using a personalized emergency action plan, and wearing medical identification (Figure 5).

For prevention of recurrences, a patient who has been treated for anaphylaxis should be evaluated by an allergy/immunology specialist who will confirm the trigger(s) by using skin tests, measurement of allergen-specific IgE levels, and other investigations as indicated. Skin tests are performed at least 3-4 weeks after the anaphylactic episode and if negative in a patient with a strong history of anaphylaxis, they should be repeated weeks or months later. Information about avoidance of relevant triggers should be provided. If applicable, immune modulation using allergen specific immunotherapy or drug desensitization protocols should be initiated. Co-morbidities such as asthma or cardiovascular disorders should be optimally managed (Figure 5).

Anaphylaxis research is no longer hindered by the perception that the disease is rare, by absence of an acceptable definition, or by lack of validated diagnostic clinical criteria. A global agenda for anaphylaxis research has been developed to improve understanding of epidemiology, patient risk factors, mechanisms and triggers, and optimal methods of diagnosis, management, and prevention.

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7 DRUG ALLERGY

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KEY MESSAGES

- Drug hypersensitivity reactions (DHRs) comprise 15 % of all adverse drug reactions and affect more than 7 % of the general population
- The term "drug allergy" is reserved to immunologically-mediated DHRs with direct or indirect evidence of drug-specific antibodies or T-cells
- Clinical presentations are classified as immediate and non-immediate reactions; the first category is mostly IgE-mediated, whereas the latter is specific T cell-mediated
- Both under-diagnosis (due to under-reporting) and over-diagnosis (due to an over-use of the term “allergy”) are common.
- The diagnostic work-up of DHRs is a step-wise approach, starting with an as exhaustive as possible clinical history, followed, when validated, by *in vivo* (skin and provocation) tests and in some rare cases by *in vitro* biological tests

Adverse drug reactions (ADRs) resembling clinically to allergy are called drug hypersensitivity reactions (DHRs). They comprise 15% of all ADRs and affect more than 7 % of the general population. The term "drug allergy" is reserved to immunologically-mediated DHRs, after showing direct or indirect evidence of either drug-specific antibodies or T-cells. These reactions are mostly unpredictable. They can be life threatening, may require or prolong hospitalization and necessitate changes in subsequent therapy. They are of significant concern for clinicians and patients.

Even though urticaria and maculopapular eruptions are the most frequent manifestations, there are many other clinical presentations artificially classified into two types (Figure 1), according to the delay of onset of the reaction after the last administration of the drug:

1) **Immediate reactions**, occurring less than 1 hour after the last drug intake, usually in the form of isolated urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastro-intestinal symptoms (nausea, vomiting, diarrhea), or anaphylaxis with or without cardiovascular collapse (anaphylactic shock) and

2) **Non-immediate reactions**, with variable cutaneous symptoms occurring after more than 1 hour and up to several days after the last drug intake, such as late-occurring urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, blistering diseases (such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) and generalized bullous fixed drug eruptions), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and symmetrical drug-related interstriginous and flexural exanthemas. Internal organs can be affected either alone or with cutaneous symptoms and include hepatitis, renal failure, pneumonitis, anemia, neutropenia, and thrombocytopenia. The first category is mostly mediated through specific IgE, whereas the latter is specific T cell-mediated.

Both under-diagnosis (due to under-reporting) and over-diagnosis (due to an over-use of the term “allergy”) are common. The diagnostic work-up of DHRs is a step-wise approach, starting with an

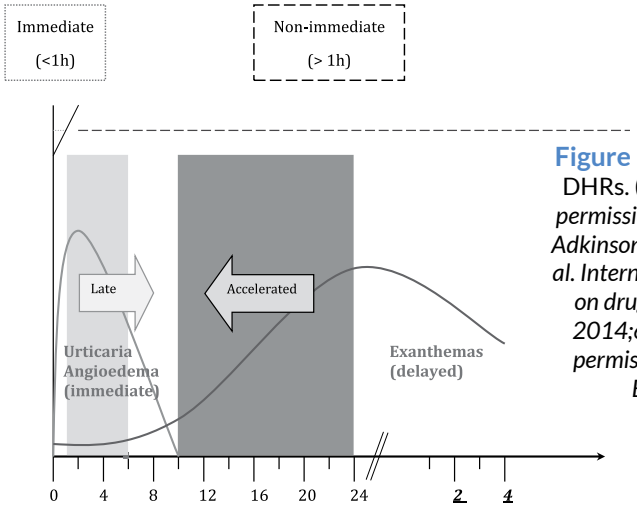

Figure 1 Chronology of DHRs. (*Reproduced with permission from Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. Allergy 2014;69:420-37, with permission from Willey Blackwell.*)

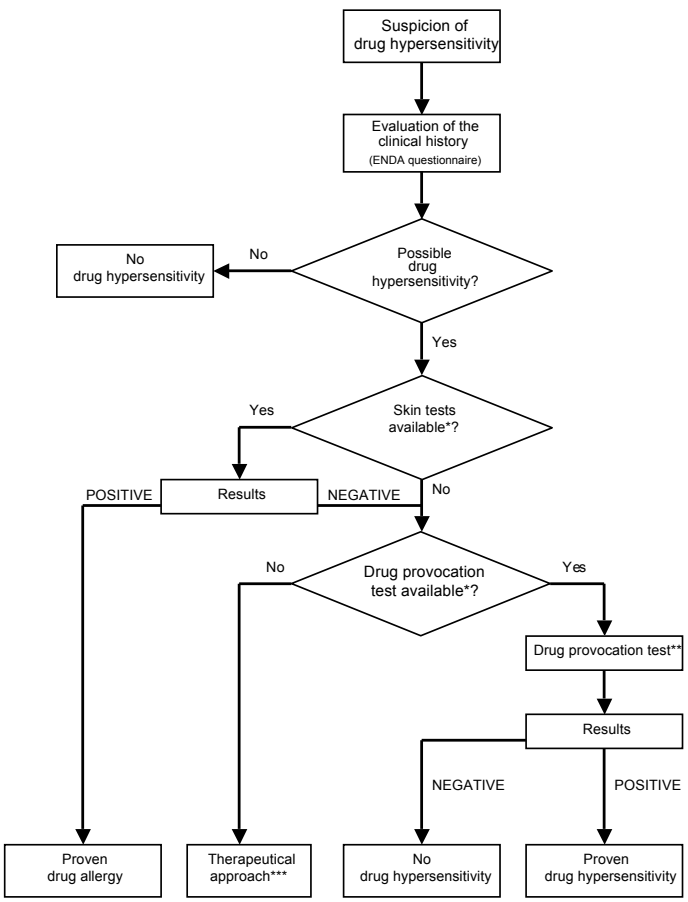

Figure 2 Flow chart when assessing DHRs. *Currently available biological tests to diagnose drug allergy lack sensitivity.**In the absence of contraindications. ***If no alternative is available (e.g., NMBA, chemotherapeutic drugs), readministration of the drug is allowed under close surveillance, considering premedication and/or desensitization. (*Reproduced with permission from Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. Allergy 2014;69:420-37, with permission from Willey Blackwell.*)

as exhaustive as possible clinical history, followed, when validated for some drug classes, by *in vivo* (skin and provocation) tests and in some rare cases by *in vitro* biological tests.

Several guidelines and consensus documents on general or specific drug class-induced DHRs are available to support the diagnosis. The recent International Consensus (ICON) on Drug Allergy synthesizes multiple guidelines into one generally approved and accepted consensus document. It provides guidance for firm diagnosis and solutions to find alternatives when the responsibility of the drug is confirmed (Figure 2). Only a thorough diagnostic work-up will allow a better classification of the reactions and provides patients with more reliable information and recommendations for future treatments. A lot still needs to be done to understand better DHRs and diagnose severe cutaneous reactions for which drug provocation tests are contraindicated and in the field of biological diagnosis.

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8 FOOD ALLERGY

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KEY MESSAGES

- Food allergy can result in considerable morbidity, impairment of quality of life & costs
- Life-threatening anaphylaxis can complicate the course of food allergy
- The point prevalence of self-reported food allergy is approximately six times higher than challenge proven food allergy
- Presence of allergen-specific IgE indicates sensitization, whereas a clinical allergic reaction can be proven only by oral food challenges
- Management includes avoidance of the offending food, insurance of a sufficient diet and education e.g. as regards behavioral approaches to avoid allergens and management of acute reactions

Allergies to foods associate considerable morbidity, impaired quality of life and costs – and can in some instances result in life-threatening anaphylaxis. Therefore, it is important to improve awareness and access for all to a proper diagnosis and treatment to ensure a safe and good life. Adverse reactions to foods encompasses many different reactions with different mechanisms including toxic, enzymatic and hypersensitivity reactions "Food allergy" refers to the subgroup of food hypersensitivity reactions in which immunologic mechanisms have been demonstrated, whether IgE and/or non-IgE-mediated (Figure 1).

The clinical presentation of food allergy involves a large spectrum of symptoms (Table 1), triggered by ingestion of food, sometimes in very small amounts or even by inhalation and skin contact.

Although these symptoms are reported frequent in the population, if investigated appropriately often they are not caused by food allergy. In a recent systematic review, the point prevalence of self-reported food allergy was approximately six times higher than challenge-proven food allergy. The prevalence of food allergy was generally higher in children compared to adults. While the prevalence of primary food allergy appeared to be stable over time, the prevalence of secondary food allergy caused by cross-reactions of food allergens with inhalant allergens appears to be increasing.

A proper diagnosis is necessary for a sufficient and safe treatment. A careful diet history is fundamental, since it can establish the likelihood of the diagnosis and identify the potential food triggers (Table 2). Positivity of skin prick tests and specific IgE to food allergens, can determine sensitization only, and a relevant elimination diet followed by an oral food challenge test is necessary to confirm the diagnosis food allergy (Figure 2). Recently, in vitro measurement of IgE to specific components of some food allergens (compenent resolved diagnosis) has shown promising results, but further studies are necessary to validate its value and clinical relevance.

Due to the good prognosis of many food allergies with spontaneous resolution, especially in children, re-challenges should be performed regularly to detect de-

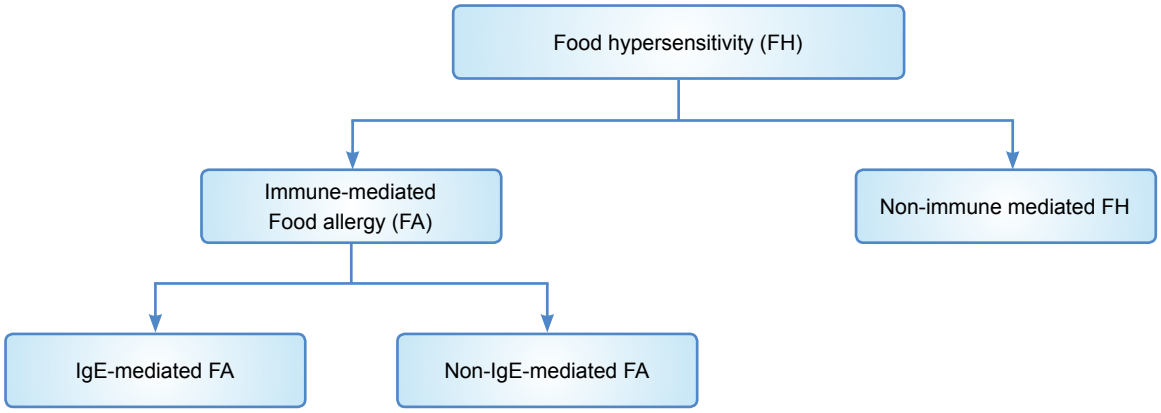

Figure 1 Food allergy - classification.

TABLE 1

Clinical features of food protein allergy		
Reactions		**Mechanism**
Cutaneous reactions	Urticaria, acute or chronic (rare) Angioedema Contact rash Atopic dermatitis	IgE and/ or non-IgE mediated
Gastrointestinal reactions	Oral allergy syndrome Nausea/vomiting Abdominal pain Diarrhea, constipation	IgE and / or non-IgE mediated
Respiratory reactions	Allergic eosinophilic gastritis, enteritis & colitis Protein-losing enteropathy	Non-IgE mediated
	Rhinoconjunctivitis Asthma Laryngeal edema	IgE and / or non-IgE mediated
Other reactions	Anaphylaxis	IgE and / or non-IgE mediated
	Food dependent exercise induced anaphylaxis	IgE and / or non-IgE mediated

TABLE 2

When to suspect food allergy
Symptoms suggestive of food allergy • Persistent symptoms, • Symptoms related to food intake • Two or more different symptoms
Especially in children with allergic predisposition

TABLE 3

Recommendations for primary prevention of food allergy
Recommendations for all infants: • No special diet during pregnancy or for the lactating mother • Exclusively breastfeeding for 4 – 6 months
Further recommendations for infants with atopic predisposition: • If supplement is needed during the first 4 months a documented hypoallergenic formula is recommended
Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity

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velopment of tolerance.Studies on possible prevention of development of food allergy have shown that simple dietary measurements in infancy can reduce the risk for food allergy (Figure 2, Table 3).

Figure 2 Reaction to a diagnostic oral challenge with hen's egg.

So far, the only safe treatment is identification and avoidance of the offending food. Education of the patient, families, health care professionals and others in the network around the patient on how to avoid ingesting the food and how to recognize and manage allergic reactions is important. In addition, especially in young children a nutritional balanced diet should be ensured to compensate the exclusion of the culprit food. Several new strategies such as oral immunotherapy are currently being investigated, and may prove to be useful in the future.

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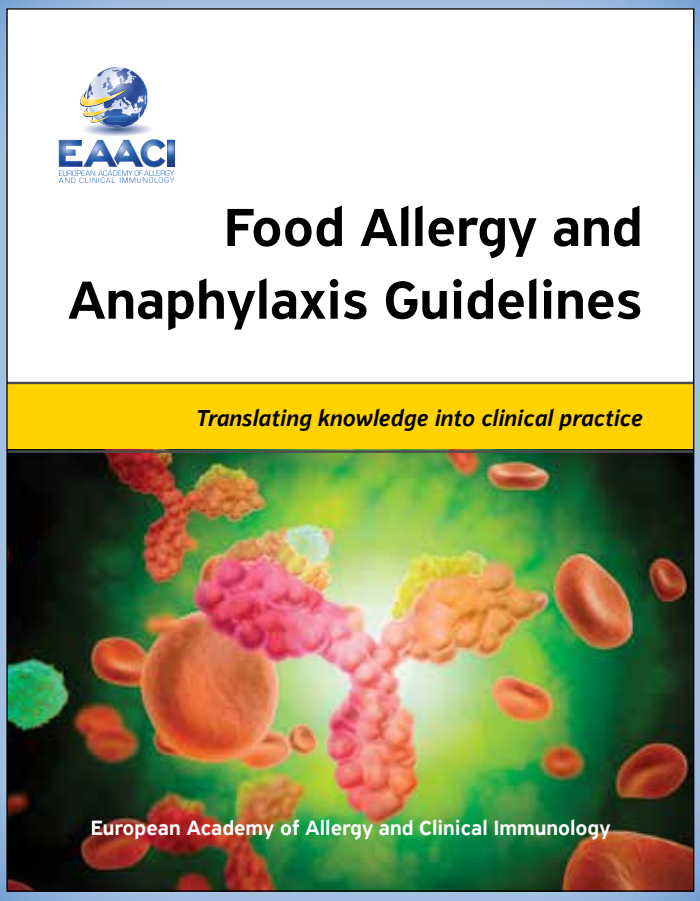

The EAACI Food Allergy and Anaphylaxis Guidelines are devoted to improve the overall caring of the patients suffering from food allergy and anaphylyaxis. The aim has been to provide scientific update on the latest evidence on the field establishing a platform where all the stakeholders could share their knowledge and ultimately create links and networks around the patients and their families. This book represents the work of over 100 individuals, health care professionals and scientists along with the involvement of both patient groups and regulators.

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9 ATOPIC DERMATITIS

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KEY MESSAGES

- Atopic dermatitis (AD) shows an increase in the worldwide prevalence
- AD is the most common chronic inflammatory skin disease and displays a complex clinical phenotype
- AD has a substantial impact on quality of life and socio-economic burden and represents an important public health
- AD often represents the first step of the atopic march and may thus offer an opportunity for disease modifying strategies

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease and may represent the very initial phase of the so-called atopic march (Figure 1). The incidence of AD has increased by two- to three-fold during the past three decades in industrialized countries. AD affects up to 20 % of the children and 2 to 10 % of adults and has a deep impact on the quality of life of patients and parents. The increasing prevalence may be linked to the Western lifestyle. AD generates a substantial economic burden. The average costs for an AD patients in Germany have been estimated to a total of about 4400€ (1450 € reimbursed direct costs, 1130€ costs not reimbursed costs and 1850 indirect costs).

Due to its complex pathophysiology, the natural history of AD is highly variable and may be determined by a number of (epi)genetic as well as environmental factors including the recently identified microbiome (Figure 2). About 30 % of the children, who have started the disease in the first weeks or months of life (early onset) will suffer from allergic rhinitis and/or asthma: the so-called the atopic march. Another half of the affected children will experience a remission before puberty (Figure 3). Social interactions, psychological adjustments, work success, sexual relationships, and quality of life often are dependent on the course of disease. Thus, the therapeutic goal should be the long-term control of the disease, i.e. the reduction of the flares and bacterial and viral complications. Disease modifying strategies should be developed to establish an optimal prevention and management during a window of opportunity in individuals at risk to experience an atopic march. These approaches will greatly benefit from the identification and validation of predictive biomarkers in the context of a stratified medicine in AD.

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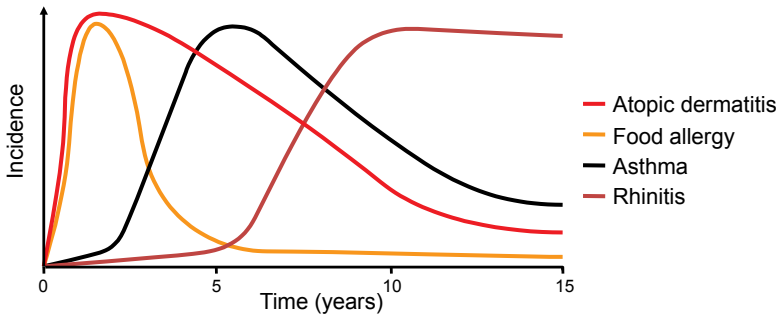

Figure 1 Atopic dermatitis is considered as the first manifestation of the atopic march. Individuals at high risk to develop allergic rhinitis and asthma could be identified at an early stage and subjected to tailored prevention and disease-modifying strategies. (*Reproduced from Br Med J, Barnetson RS, Rogers M. Childhood atopic eczema, 324, 1376-9, Copyright 2002 with permission from BMJ Publishing Group Ltd.*)

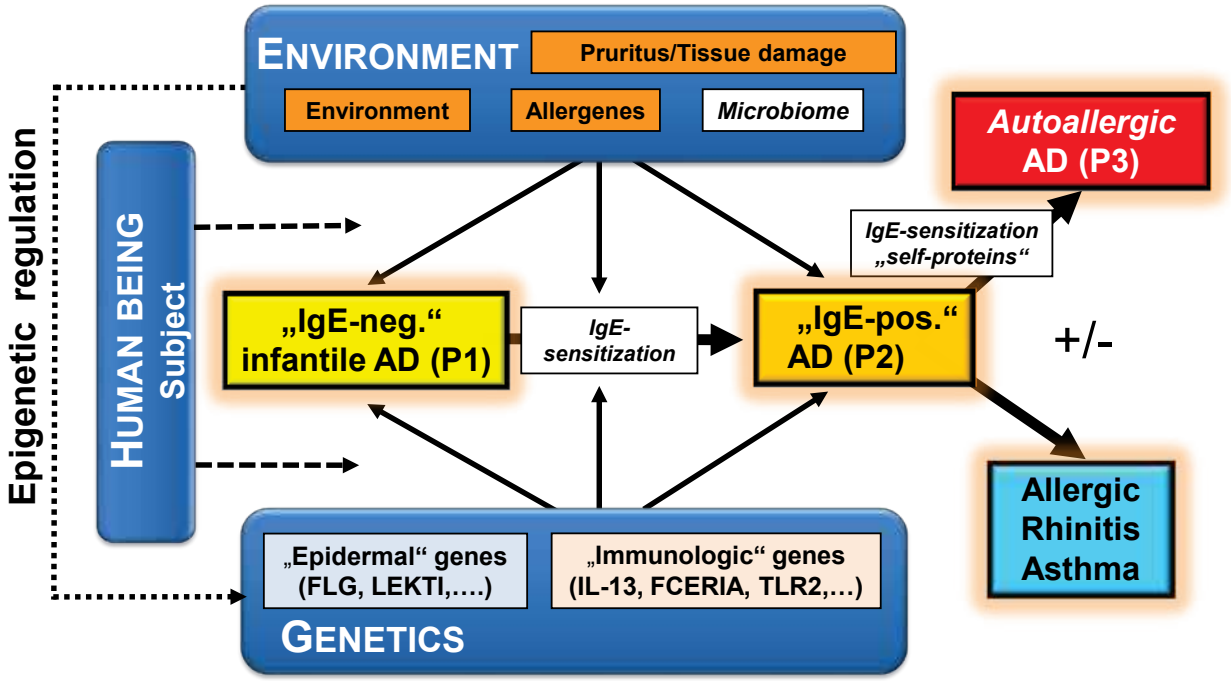

Figure 2 Atopic dermatitis is a paradigmatic chronic inflammatory skin disease where gene-gene and gene-environment interactions are involved. More recently, the role of epigenetic regulation and of the microbiome have been highlighted with the aim to focus of new prevention strategies. This figure depicts the archetypical natural history of an AD with an early onset, followed by the classic atopic march, leading to allergic rhinitis and asthma. (*Adapted from Bieber T. Atopic dermatitis. N Engl J Med 2008;358:1483-1494.*)

Courses type of AD	infantile phase 0-2 years	childhood phase 2-6 years	juvenile phase 6-14 years	adolescent phase 14-20 years	adult phase >20 years	Number of patients (n)	Percentage of patients
Subgroup I: Start of AD between birth and 2nd year of life							
1						0	0%
2						2	0.33%
3						2	0.33%
4						1	0.16%
5						**189**	**31.14%**
6						1	0.16%
7						0	0%
8						4	0.66%
9						0	0%
10						7	1.15%
11						8	1.32%
12						0	0%
13						0	0%
14						15	2.47%
15						6	0.99%
16						13	2.14%
Subgroup II: Start of AD between 2nd and 6th year of life							
17						1	0.16%
18						0	0%
19						0	0%
20						**84**	**13.84%**
21						0	0%
22						7	1.15%
23						6	0.99%
24						3	0.49%
Subgroup III: Start of AD between birth and 6th and the 14th year of life							
25						0	0%
26						0	0%
27						**58**	**9.56%**
28						9	1.48%
Subgroup IV: Start of AD between 14th and the 20th year of life							
29						2	0.33%
30						**77**	**12.69%**
Subgroup V: Start of AD after the 20th year of life							
31						**112**	**18.45%**

Figure 3 Heterogeneity of the natural history of AD. Prevention and therapeutic strategies must be adapted to the individual situations. Reliable predictive biomarkers represent an unmet need in the stratification of AD patient-tailored intervention. (*Reproduced with permission from Garmhausen D, Hagemann T, Bieber T,et al. Characterization of different courses of atopic dermatitis in adolescent and adult patients. Allergy 2013;68:498-506, with permission from Willey Blackwell.*)

10 URTICARIA

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KEY MESSAGES

- Urticaria is a common disease with marked influence on quality of life
- Urticaria should be divided into acute and chronic, spontaneous or inducible, with emphasis on possible eliciting factors
- The key cell involved is the mast cell, which can be activated by a vast variety of stimuli and the major mediator is histamine
- Urticaria can be treated efficiently without significant side effects in the vast majority of patients, children or adults
- Non-sedating antihistamines, sometimes in doses up to four times the recommended dose, are the mainstay of treatment

Urticaria is a common, heterogeneous group of disorders with a large variety of underlying causes. It is characterized by the appearance of fleeting wheals, each lasting 1–24 hours and/or angioedema lasting up to 72 hours. The key cell involved is the mast cell, which can be activated by a vast variety of stimuli. Activation of superficially situated mast cells in the skin gives rise to urticaria, whereas mast cells in dermis are involved in angioedema. Often both manifestations are present in the same patient. Histamine is the key mediator in urticaria and most cases of angioedema, whereas bradykinin is responsible for some types of angioedema (hereditary angioedema and Angiotensin- Converting-Enzyme (ACE) induced angioedema).

It is estimated that up to 25% of adults will experience at least one episode of acute urticaria sometime in their lifetime, while only around 3% will develop chronic spontaneous urticaria (point prevalence 0.6%). In children, urticaria appears to be less common (3-5 %) with chronic urticaria being much less prevalent. Very little is known on the natural history of the disease, but the duration is most often less than 5-10 years. Quality of Life in the patient is often severely affected.

International guidelines divide urticaria in acute and chronic (with an arbitrary limit set at 6 weeks of duration) and in *spontaneous* forms (without a known underlying cause except autoantibodies directed against the receptor for IgE) and *inducible forms* (Tables 1 and 3).

The diagnosis is easily made in typical cases, but a thorough medical history is critical both for correct classification and for avoidance of extensive investigations for underlying disease. Normally, a test for autoimmune urticaria with autologous serum or via in vitro tests together with investigations for a chronic infection is sufficient. Urticaria can, however also be a feature of more severe diseases and should not be overlooked. The severity of the disease is assessed according to the score system presented in Table 2. Since disease, severity is often fluctuating during the day, a 24-hour score is advised, Table 2.

In the inducible forms, the treatment of choice (but not always possible) is avoidance. Pharmacological treatment can in the majority of the cases be confined to non-sedating antistamines in doses up to four times the recommended dose (Figure 1). Treatment should be on an every day basis in more severe cases and

TABLE 1

Urticaria classification			
Type	**Subtype**	**Definition**	**Comments**
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous wheals for < 6 weeks	Can be associated with concomitant diseases such as chronic infections or thyroid diseases, but causality is only rarely established
	Chronic spontaneous urticaria	Spontaneous wheals for > 6 weeks	
		The single wheal disappears within 24 hours. Longer standing wheals are a feature of urticaria vasculitis	
Inducible urticaria	Acute, but may be recurrent even on an everyday basis	Wheals induced by a defined, external or internal stimulus	See Table 3

TABLE 2

Severity Scoring		
Score	**Wheals**	**Pruritus**
0	None	None
1	Mild (< 20 wheals in 24 hours)	Present (but not annoying nor troublesome)
2	Moderate (20-50 wheals in 24 hours)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Severe (>50 wheals in 24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score 0-6; Reproduced with permission from ZuberbierT,Asero R, Bindslev-Jensen C,et al.EAACI/GA(2) LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria, Allergy 2009;64:1417-26, with permission from Willey Blackwell.

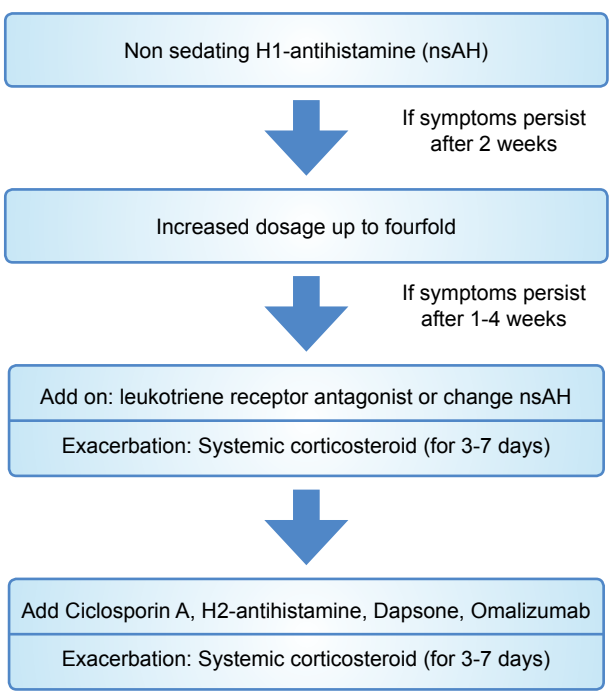

Figure 1 Treatment algorithm for chronic urticaria. (*Reproduced with permission from ZuberbierT,Asero R, Bindslev-Jensen C,et al.EAACI/GA(2) LEN/EDF/WAO guideline: management of urticaria, Allergy 2009;64:1427-43, with permission from Willey Blackwell.*)

TABLE 3

Inducible urticaria (acute forms)		
	Stimulus	**Comments**
Physical urticaria	Cold contact Heat contact Vibration UV light Pressure	Typically wheals are elicited immediately except in delayed pressure urticaria, where symptoms are elicited hours after stimulus.
Allergic urticaria	Food (peanut, nuts, milk, egg) Drugs (penicillin, aspirin) Insect venom (wasp, honey bee)	Often elicited in combination with other allergic symptoms and signs such as asthma, rhinitis, gastro-intestinal symptoms or anaphylaxis.
	Skin contact with allergen	Including skin testing with allergen. Also elicited by urticariogenic substances
	Food and physical exercise	Food-dependent, exercise-induced anaphylaxis: only elicited by a combination of food intake (wheat) and physical exercise
Infection	Acute infection (most often virus)	Commonly seen in children with acute infection, much less frequent in adults
Other types	Water	Aquagenic urticaria
	Rise in body core temperature	Cholinergic urticaria (pin point wheals)
	Exercise (without food intake)	Exercise induced urticaria (or anaphylaxis)

only as needed in milder forms.

Omalizumab, originally registered as a drug for treatment of asthma has recently been approved for urticaria also and has demonstrated very promising efficacy in recalcitrant cases of urticaria.

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11 EAACI - GA²LEN - EDF - WAO GUIDELINE ON URTICARIA

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KEY MESSAGES

- The 2013 revisions and update of the EAACI/GA²LEN/EDF/WAO guidelines is based on the GRADE methodology
- The impact on quality of life should be measured. Urticaria can be highly debilitating: reduction of productivity reaches 25-30% in moderate to severe cases and there is a major impact on sleep.
- Urticaria treatment is based on a step up algorithm with first line non-sedating antihistamines
- The aim of treatment is the complete absence of symptoms
- Areas of further research in urticaria are underlined

The EAACI/GA²LEN/EDF/WAO guidelines on urticaria were launched in 2009. Following a consensus conference held in 2012 in Berlin, a joint initiative of the European Academy of Allergy and Clinical Immunology (EAACI) Dermatology Section, Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) performed a systematic literature review using the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) methodology. The 2013 revised EAACI/GA²LEN/EDF/WAO guidelines are the result of the above. The strength of a recommendation and the quality of supporting evidence were assessed independently by two assessors for each recommendation. They took into consideration as negative/risk: side-effects (graded on severity) and costs; and as benefits: reduction in urticaria symptoms and improvement in quality of life (QoL). The GRADE system permits strong recommendations supported by low- quality evidence from downgraded RCTs or observational studies. On the other hand, weak recommendations may be based on high-quality evidence if other factors are important, for example the price of a treatment option.

All aspects of the disease were critically evaluated using the GRADE methodology: definition, clinical aspects, diagnostic work-up, assessment of disease activity and impact, and management. Ideally, the diagnostic work up in chronic urticaria (CU) (Figure 1) reveals a cause that can be treated, but frequently this is not possible. Especially the inducible forms of CU are mainly idiopathic. It is strongly advised to search for underlying causes in chronic spontaneous urticaria only in patients with longstanding and/or severe disease and to perform extended diagnostic testing based on the patient history.

Aiming for complete symptom control in urticaria as safely as possible is recommended. Treatment with non sedating H1-antihistamines is the first line option (safety data are available for their use for several years continuously). Continuous use is superior to on demand use, as antihistamines block the development of new wheals and angioedema, but do not help to decrease the time to resolution of already existing ones.

It is recommended not to use older first generation antihistamines, because they have pronounced adverse events. For example, they can interfere with rapid eye movement (REM) sleep and impact on learning and performance. As shown by a recent head to head trial, there are no benefits from non

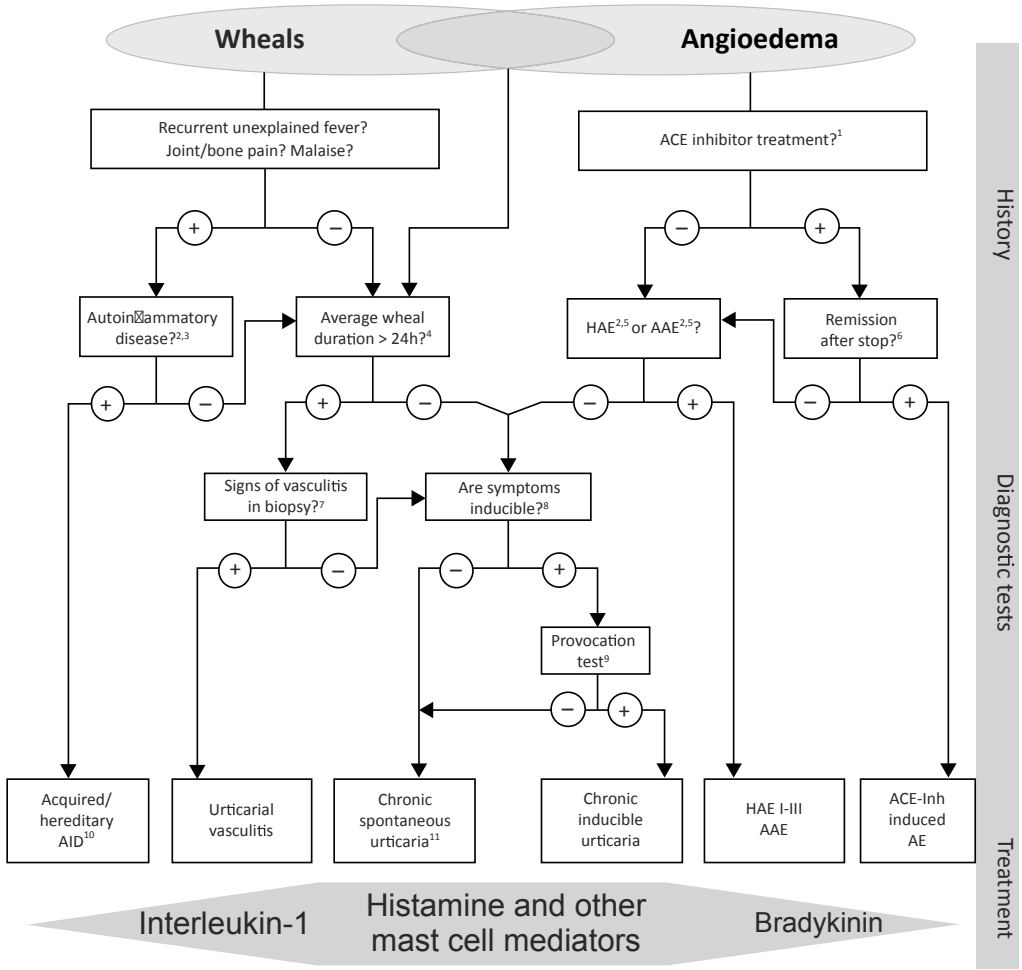

Figure 1 Diagnostic algorithm for patients presenting with wheals, angioedema, or both. AAE: Acquired angioedema due to C1-inhibitor deficiency; ACE-Inh: angiotensin converting enzyme inhibitor; AE: angioedema; AH: Antihistamine; AID: Auto-inflammatory disease; HAE: Hereditary angioedema; IL-1: Interleukin-1. [1] Other (new) drugs may also induce bradykinin-mediated angioedema. [2] Patients should be asked for a detailed family history and age of disease onset. [3] Test for elevated inflammation markers (C-reactive protein, erythrocyte sedimentation rate), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy; perform gene mutation analysis of hereditary periodic fever syndromes (e.g. Cryopyrin-associated periodic syndrome), if strongly suspected. [4] Patients should be asked: "How long do your wheals last?". [5] Test for Complement C4, C1-INH levels and function; in addition test for C1q and C1-INH antibodies, if AAE is suspected; do gene mutation analysis, if former tests are unremarkable but patient's history suggests hereditary angioedema. [6] Wait for up to 6 months for remission; additional diagnostics to test for C1-inhibitor deficiency should only be performed, if the family history suggests hereditary angioedema. [7] Does the biopsy of lesional skin show damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of UV (urticarial vasculitis)? [8] Patients should be asked: "Can you make your wheals come?". [9] In patients with a history suggestive of inducible urticaria standardized provocation testing according to international consensus recommendations should be performed. [10] Acquired AIDs (autoinflammatory syndromes) include Schnitzler´s syndrome as well as systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD); hereditary AIDs include Cryopyrin associated periodic syndromes (CAPS) such as familial cold auto-inflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID), more rarely hyper-IgD syndrome (HIDS) and tumor necrosis factor receptor alpha-associated periodic syndrome (TRAPS). [11] In some rare cases recurrent angioedema is neither mast cell mediator-mediated nor bradykinin-mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as "idiopathic angioedema" by some authors. (*Reproduced with permission from Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis and management of Urticaria, The 2013 revision and update. 2014 Apr 30. doi: 10.1111/all.12313. [Epub ahead of print], with permission from Willey Blackwell.*)

TABLE 1

Areas of further research in urticaria
• Global epidemiology, in adults and children
• The socio-economic consequences
• Identification of mast cell/basophil activating factors
• Identification of new histological markers
• Identification of serum biomarkers of urticarial activity/mast cell activation
• Determination of minimal important differences for instruments that assess disease activity or impact relevant response (e.g., UAS, CU-Q2oL)
• Clarification of the role of coagulation/coagulation factors in CSU
• Development of commercially available in vitro tests for detecting serum auto-antibodies for anti-IgE or anti-FcεRI
• Clarification of associated psychiatric/psychosomatic diseases and their impact
• Pathomechanisms in antihistamine-resistant urticaria/angioedema
• Double-blind control trials comparing different modern second- generation anti-H1s in higher doses in CSU and different subtypes of urticaria
• Regular v. on demand use of anti-H1 antihistamines on the duration of urticaria/severity of urticaria
• Multicenter studies on the possible effect of anticoagulants (oral and heparin derivatives) on CSU
• Controlled multicenter trials on the possible effect of add-on of anti-H2, montelukast, sulfone, methotrexate, azathioprine

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sedating antihistamines regarding efficacy including improvement of quality of sleep.

The second line treatment option in CU is updosing of non-sedating second generation antihistamines. This has been verified in studies using up to fourfold higher than recommended doses of bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, and rupatadine.

The recommended third line treatment is to use omalizumab, cyclosporin A or montelukast as an add-on therapy to fourfold antihistamine treatment. Of these options, omalizumab is the only treatment licensed for chronic spontaneous urticaria, whereas cyclosporin A, where the level of evidence is also good, as well as montelukast, remain off-label. This is also the case for numerous other therapies that are not well-proven to be efficacious.

Patient-related outcomes are important to be looked at in the management for urticaria. The available data indicate that urticaria has a detrimental effect on both objective functioning and subjective wellbeing. In one study, health status scores in patients with chronic spontaneous urticaria (CSU) were comparable to those reported by patients with coronary artery disease. The extent and nature of disability shows a large variation within different urticarial subsets. A QoL Questionnaire (CU-Q2oL), specifically developed for CSU, was validated, including for physical, emotional, social, and practical aspects characteristic of this condition. Another questionnaire (AE-QoL) covers patients with angioedema. There is a strong recommendation for both this questionnaires.

The panel and participants identified several areas in which further research in urticaria is needed (table 1).

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12 ANGIOEDEMA

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Angioedema is defined as localized and self-limiting swelling of the subcutaneous and submucosal tissue, due to a transient increase in vascular permeability caused by the release of vasoactive mediators (Figure 1). It frequently occurs simultaneously with urticaria (the so called urticaria-angioedema syndrome) with the concomitant appearance of wheals and angioedema. Urticaria and angioedema share the same pathophysiological events including an acute vasodilation of small vessels and an increase in vascular permeability leading to extravasation of plasma and macromolecules in the superficial dermis (urticaria) or deep dermis and subcutaneous tissue (angioedema).

Figure 1 A typical angiodema of the lips in a child with hereditary angioedema.

KEY MESSAGES

- Angioedema can be hereditary or acquired and is characterized by recurrent, acute episodes of cutaneous or mucosal swelling, more frequently of the face and neck
- Angioedema is one of the most frequent clinical manifestations of allergy and is often associated with drug, food or hymenoptera venom hypersensitivity
- Vasoactive mediators including histamine, bradykinin, leukotrienes, prostaglandins and platelet activating factor (PAF), are involved in the pathogenesis of angioedema
- Most attacks of angioedema are limited to the skin, but in some cases severe abdominal symptoms or life-threatening laryngeal angioedema may occur
- Different forms of angioedema respond to specific therapies and, therefore, precise diagnosis of the type of angioedema is mandatory for implementing an effective prevention and treatment

Angioedema is becoming a very frequent clinical emergency and it is the second cause of hospitalization after asthma as an allergic disorder. The current classification of angioedema identifies both hereditary and acquired forms of the disease. Hereditary angioedema (HAE) is due to deficiency of C1 inhibitor (C1INH) a plasma protein that controls activation of the kinin system, the complement pathway and coagulation (Figure 2). Deficiency of C1INH leads to uncontrolled generation of bradykinin, a potent vasoactive mediator that is responsible for HAE attacks. Rare forms of HAE with normal C1INH have been associated with activating mutations of Factor XII, the trigger of the bradykinin cascade. Acquired forms of angioedema include those associated with allergic reactions, mostly induced by drugs, food or hymenoptera stings. These forms of allergic angioedema are due to vasoactive mediators such as histamine, prostaglandins, leukotrienes and platelet activating

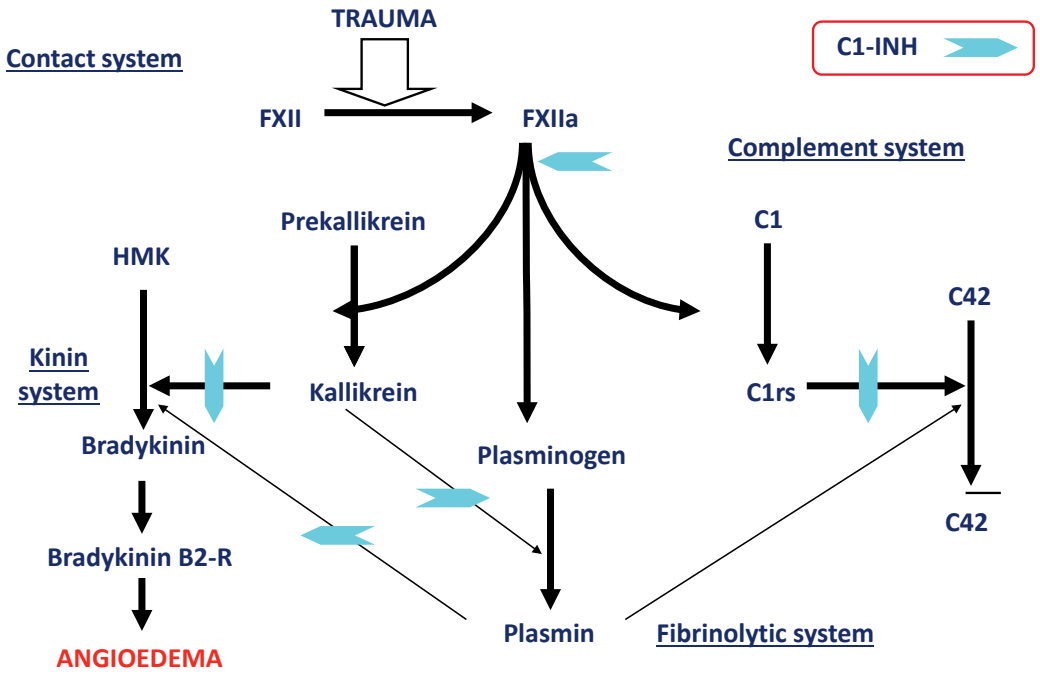

Figure 2 Mechanisms of angioedema due to C1 inhibitor (C1-INH) deficiency. Arrows indicate the biochemical steps controlled by C1-INH in the complement cascade, the kinin pathway and the fibrinolytic system. The generation of activated Factor XII (Factor XIIa), induced by local trauma, results in the conversion of prekallicrein into the active enzymatic form of kallicrein. This enzyme acts on high molecular weight kininogen (HMK) and generates bradykinin, a small peptide that induces angioedema by interacting with specific B2 receptors (bradykinin B2-R) expressed on endothelial cells and smooth muscle cells of small vessels.

factor (PAF) released by activated mast cells. Two other variants of acquired angioedema are mediated by bradykinin and include those due to an acquired deficiency of C1INH, frequently associated with hematologic tumors, and angioedema induced by ACE inhibitors. ACE is a key enzyme responsible for bradykinin inactivation and its blockade by ACE inhibitors, a commonly used class of antihypertensive agents, may trigger acute attacks of angioedema in genetically predisposed individuals. In many patients, however, the cause of angioedema remains unknown and they are defined as having "idiopathic" angioedema. Idiopathic angioedema can be either histaminergic or non-histaminergic depending on whether antihistamines prevent it.

Regardless of its cause and whether hereditary or acquired, angioedema is clinically characterized by recurrent swelling of the face (mostly eyelids and lips), neck, upper or lower extremities and external genitals. Mucosal angioedema is most frequently localized to the mouth (tongue and uvula), the gastrointestinal tract, with severe abdominal pain resembling an acute abdomen syndrome, or to upper respiratory tract. Laryngeal angioedema is the most severe location and may lead to death if not treated rapidly and appropriately.

Even though allergic angioedema and angioedema due to C1INH deficiency have similar clinical features, their treatment is remarkably different. Attacks of allergic angioedema usually respond to antihistamines, glucocorticoids and epinephrine (if part of anaphylaxis), whereas those due to C1INH deficiency require treatment with C1 inhibitor (replacement therapy), ecallantide (a kallicrein inhibitor) or icatibant, a bradikinin B2 receptor antagonist. Table 1 summarizes the main clinical clues and the diagnostic tests to differentiate between the two main forms of angioedema. A rapid recognition of the type of angioedema and a precise diagnosis is mandatory to initiate an appropriate treatment and to prevent life-threatening attacks of laryngeal angioedema.

TABLE 1

Main clinical features, diagnostic tests and treatments of allergic angioedema and angioedema due to deficiency of C1 INH

	Allergic (e.g. Anaphylaxis)	C1 Inhibitor Deficiency (e.g. HAE)
Urticaria	+	-
Course	Rapid (min)	Slow (hours)
Duration	12 - 24 h	48 - 72 h
Laryngeal Edema	+/-	+
Bronchospasm	Frequent	Absent
Abdominal Pain	Rare	Frequent
Hypotension	+	-
Diagnostic Test	Tryptase	C1 Inhibitor (functional) C4
Treatment	Epinephrine Antihistamines Steroids	C1 inhibitor Icatibant Ecallantide

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13 ALLERGIC CONTACT DERMATITIS

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KEY MESSAGES

- Allergic contact dermatitis is a T-cell mediated, delayed-type hypersensitivity reaction in the skin, with skin-infiltrating, CD3+ CD4+ T helper cells
- The clinical features depend on the type of responsible allergens: usually, dermatitis occurs at the site of allergen application, but spreading of the dermatitis is possible
- A good history and patch testing are the mainstays for diagnosis
- The management consists of the elimination or the reduction of contact allergens and the use of a topical steroid or of a topical calcineurin inhibitor
- Up to 70% of patients sensitized to wide-spread allergens will have some degree of chronic dermatitis

Allergic contact dermatitis (ACD) is a typical manifestion a T-cell mediated, delayed-type hypersensitivity reaction in the skin. Most allergens in allergic contact dermatitis are so-called haptens of low molecular weight and need to link with proteins (carriers) in the skin, before they become antigenic. ACD is not related to atopy, however, patients with atopic dermatitis develop epicutaneous sensitizations more frequently as compared to non-atopic individuals, probably due to the related barrier defect of the skin.

CD3+ CD4+ T helper are the major skin-infiltrating cells. The role of skin-infiltrating CD8+ T cells is not clear yet, but a subpopulation of these cells may function as suppressor cells, which dampen down the reaction. Spontaneous resolution occurs after the antigen is removed and the T-cell mediators disappear. A number of cells (e.g. naïve or induced Tregs) and molecules (e.g. IL-10, prostaglandin E) are involved in the downregulation of the inflammatory response.

The clinical features of ACD depend on the type of responsible allergens. Usually, dermatitis occurs at the site of allergen application, but spreading of the dermatitis is possible (Figure 1a and b). Contact dermatitis caused by an airborne material may be difficult to identify, but this can occur (e.g. with plants or volatile preservatives in wall colors). If a contact allergen is ingested or inhaled it can rarely lead to hematogenous allergic contact dermatitis.

Worldwide, nickel sulfate is the leading cause of ACD. Women present more commonly than men with ACD, and there is an increase in incidence with advancing age. A good history and patch testing (Figure 2) are the mainstays in the diagnosis of allergic contact dermatitis. In taking the patient's history, it is important to consider occupational, household, and recreational exposure to possible allergens. Once there is a suspicion of ACD, patch testing is indicated. The European baseline series from the European Society of Contact Dermatitis is a recommendation of a minimum set of allergens to which European patients should be tested (http://www.escd.org/aims/standard_series/). These can be adapted to regional occurences of contact allergens and can be monitored to estimate incidence of contact sensitzations to individuals allergens. According to the history, a more extensive allergen set shall be applied, if ACD is suspected.

Figure 1 a - Nickel allergy induced by a nickel containing jeans button; b - Chronic hyperkeratic allergic contact dermatitis to chromium. Irritant contact dermatitis is an important differential diagnosis.

Figure 2 Patch testing and a positive patch test reaction.

The management of all types of suspected ACD consists of the elimination or the reduction of contact allergens and the use of a topical steroid or – particularly in sensitive areas (face, intertriginous sites) – a topical calcineurin inhibitor to return the skin to a normal state. Allergen avoidance can be simple or virtually impossible at other times. Unfortunately, up to 70% of patients sensitized to wide-spread allergens will still have some degree of dermatitis after some years.

Physicians who perform patch testing must be able to communicate to the patient materials, which may contain offending allergens. The identification of a causative occupational contact allergen, which may be avoided thereafter can help to keep a patient at a workplace. It is recommended that the patient gets an 'allergy passport' with information about identified allergens.

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14 LATEX ALLERGY

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Latex allergy emerged as a major public health problem in the 1980's from the widespread use of latex gloves in the healthcare setting to protect against the transmission of viral infections, including hepatitis and human immunodeficiency virus, on a background of a rising prevalence of atopic disease. The presentation of IgE-mediated Type I latex allergy ranges from mild itching and erythema at the site of skin or mucosal contact, localised urticaria (Figure 1) to anaphylaxis. This diverse spectrum of reactions has been referred to as the contact urticaria syndrome.

Individuals at risk of immediate hypersensitivity reactions to latex include health care workers, dentists, patients with spina bifida requiring long term catheterisation, those with atopy or hand dermatitis and workers in the rubber industry. Wearing powdered gloves appears to increase the risk of allergic sensitisation substantially and these have been banned in most healthcare settings in favour of non-powdered gloves and non-rubber alternatives, including vinyl and nitrile. Coupled with the adoption of stringent corporate measures to identify and avoid

KEY MESSAGES

- Allergy to natural rubber latex protein can result in a spectrum of presentations from localised erythema and burning to contact urticaria and anaphylaxis
- Individuals at risk of developing latex allergy are atopics, healthcare and rubber industry workers and patients with spina bifida
- Allergic reactivity depends on the IgE sensitization profile to latex proteins in rubber
- The latex allergy epidemic starting in 1980's has been controlled by measures to identify and avoid products containing latex in at risk settings and removal of powdered latex gloves from the workplace

Figure 1 Contact urticaria due to a household rubber glove.

TABLE 1

Risk minimization measures for latex allergy in operating theatres
• Identify patients at risk by pre-operative assessment (history, measurement of specific IgE and skin prick testing)
• Clear identification of at risk patients in theatres (ID bracelet and chart alerts)
• Careful pre-operative assessment by the anaesthetist
• First on the morning list for operations
• Avoidance of all latex products, including gloves, catheters, anaesthetic equipment, giving sets with natural rubber latex ports, vials and syringes with rubber stoppers
• Resuscitation facilities immediately available.

latex exposures in risk settings (Table 1) and the reduction of leachable latex protein in personal products has reduced the 'latex epidemic' to manageable proportions in most settings, although it is likely to remain a potential problem for many more years, because sensitisation is probably lifelong.

Developing allergic contact dermatitis to chemicals used in the manufacture of rubber products (type IV hypersensitivity), including rubber accelerators, and the risk of irritant contact dermatitis through prolonged glove wearing remains a problem in some occupations, including dentistry, hairdressing, mechanics and manufacturing industry.

Natural rubber latex is harvested from the rubber tree, *Hevea braziliensis*, which is indigenous to the Amazon region, but mainly cultivated in Malaysia and Thailand. Latex forms the cytoplasm of specialized cells called lacticifers that function to seal damaged sites. It contains water, rubber (cis-1,4-polyisoprene), protein, resins, sugars, ash and sterol glycosides.

In adult latex allergic patients, prohevein (Hev b 6.01), hevein (Hev b 6.02), rubber elongation factor (Hev b 1) and Hev b 5 are important allergens. In children with spina bifida or those with a history of multiple operations, Hev b 1 and rubber elongation factor homologue (Hev b 3) are important. Hev b 8, on the other hand is a profilin with high cross-reactivity to many species of tree (including silver birch), grass, vegetable and some fruits (the latex-fruit syndrome). IgE against Hev b 8 was the commonest mono-sensitisation on microarray in a series of 41 patients with elevated specific latex IgE, but only one of them showed symptoms, illustrating that clinical latex allergy depends on the sensitization profile to the different latex proteins in rubber.

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15 INSECT STING ALLERGY

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KEY MESSAGES

- Hymenoptera stings may cause systemic reactions of varying severity up to fatal anaphylaxis
- Several new factors influencing the severity of hymenoptera sting reactions in untreated patients have been identified
- Component resolved diagnosis might greatly enhance the accuracy of the diagnosis, allowing physicians to optimize patient selection for immunotherapy
- Subcutaneous venom immunotherapy is the only effective treatment for hymenoptera venom allergic patients and also improves health-related quality of life
- The general population and healthcare workers need to be made more aware of the disease and the availability of venom immunotherapy

Hymenoptera stings are responsible for significant morbidity and deterioration in health-related quality of life (HRQL) due to the allergic reactions they cause, ranging from large local reactions (LLRs) to the most severe systemic reactions (SR), which can culminate in fatal anaphylaxis. The offending hymenoptera belong to the suborder Aculeate, which are made up of the Apoidea (*Apis mellifera* and *Bombus* species) and Vespidae (*Vespinae* and *Polistinae* subfamilies) (Figure 1). In the USA, stinging hymenoptera also include the fire ant (*Solenopsis invicta*), and in Australia, the jack jumper ant (*Myrmecia pilosula*). Worldwide epidemiological studies report a prevalence of SRs between 0.3 % and 8.9 %, with anaphylaxis reported in 0.3–42.8% of cases. The prevalence of SRs in paediatric subjects seems to be lower.

To date, there is no existing parameter that enables clinicians to predict, who will have a future reaction and whether it will be a LLR or generalized anaphylaxis. Several concomitant factors, which include the environment, genetics and individual elements, may account for the occurrence and the severity of a SR (Table 1).

The skin tests (usually intradermal) continue to play a fundamental role in the diagnosis of venom allergy. Component resolved diagnosis might greatly enhance the accuracy of the diagnosis, allowing physicians to optimize patient selection for immunotherapy, especially in 'double-positive' patients. However, some relevant venom allergens are not commercially available in the recombinant form. Additional tests (like basophil activation test) are restricted to laboratories with expert technicians for the moment.

Patients with a history of a systemic reaction are strongly advised to carry emergency kits containing self-injectable epinephrine and to refer to an allergy specialist for evaluation and consideration of venom immunotherapy (VIT).

Subcutaneous VIT is a highly effective treatment, which is designed to reduce the risk of a subsequent SR, prevent morbidity and also improve HRQL. While there is a strong consensus that VIT is indicated for severe SRs, there is less agreement on whether adults, and especially children, with systemic cutaneous reactions are suitable candidates, as the prognosis in

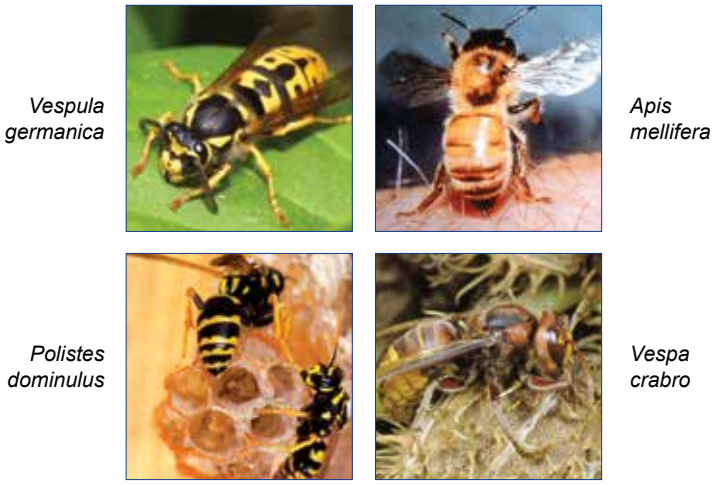

Figure 1 Pictures of Hymenoptera.

TABLE 1

Factors influencing the severity of Hymenoptera stings
• History of prior severe sting reaction (with respiratory or cardiovascular symptoms)
• Insect type (honeybee, European hornet)
• Older age
• Mast cell diseases, elevated baseline serum tryptase concentration
• Pre-existing disease (cardiovascular and respiratory diseases)
• Treatment with beta blockers, angiotensin-converting enzyme inhibitors

TABLE 2

Risk factors for side effects during VIT
• Honeybee venom
• Build-up phase
• Fast increase schedule
• Mastocytosis, elevated baseline serum tryptase concentration (build-up phase)
• Cardiovascular diseases
• Treatment with beta-blockers*, ACE-inhibitors*

** Not confirmed by all studies*

dermal reactors is usually considered to be good. A better knowledge of risk factors for VIT side effects may reduce their occurrence (Table 2).

A number of new strategies for VIT, mostly based on recombinant technologies are evaluated, as well as alternative routes for the administration of VIT, the majority of which have not yet been used in humans.

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16 OCCUPATIONAL ALLERGY

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KEY MESSAGES

- Occupational allergy is the result of an interaction between multiple genetic, environmental and behavioral influences
- Diagnosing occupational allergy is a complex undertaking, the primary goal of which is to demonstrate a causal relation between exposure to a specific agent encountered at work, allergic responses and symptoms
- A reliable diagnosis is of utmost importance for the management of patients with occupational allergy, since the treatment is essentially based on the avoidance of the allergen source
- The clinical history is a key element of the investigation of occupational allergic disorders. Immunologic tests should be performed to identify sensitization to specific occupational allergens
- Environmental control is crucial for prevention, and every effort should be made to keep the workplace without an exposure hazard

Occupational allergy refers to those disorders or conditions that are caused by exposure to substances in the work environment and in whose pathogenesis allergic factors are determinant. The allergic diseases that may be contracted as a consequence of exposure to sensitizing agents in the workplace are rhinitis, conjunctivitis, asthma, eosinophilic bronchitis, hypersensitivity pneumonitis, allergic contact dermatitis, immunologic contact urticaria and occupational anaphylaxis. When these disorders are not caused by occupational exposures, but are aggravated in the workplace the term work-exacerbated is used.

Workplace agents are complex mixtures of specific and non-specific components (Figure 1). Sensitization precedes the development of allergic symptoms, which may follow the pattern of an "occupational allergic march" (Figure 2).

Occupational rhinitis is an inflammatory disease of the nose, characterized by intermittent or persistent nasal symptoms, and/or variable nasal airflow limitation and/or hypersecretion due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace.

Occupational asthma (OA) refers to *de novo* asthma or the recurrence of previously quiescent asthma induced by either sensitization to a specific substance (eg, an inhaled protein or a chemical at work), which is termed allergic or sensitizer-induced OA, or by exposure to an inhaled irritant at work, which is termed irritant-induced OA (Figure 3). Approximately 372 different causes of allergic OA have been identified. These agents are categorized into high-molecular-weight (HMW) compounds, which are proteins acting through an IgE-mediated mechanism, and low-molecular-weight (LMW) compounds, which are chemical sensitizers that, with few exceptions, are not associated with an IgE-dependent mechanism.

Hypersensitivity pneumonitis (HP) is an allergic lung disease that occurs as the result of an immunologic inflammatory reaction to the inhalation of any of a variety of organic dusts or LMW chemicals

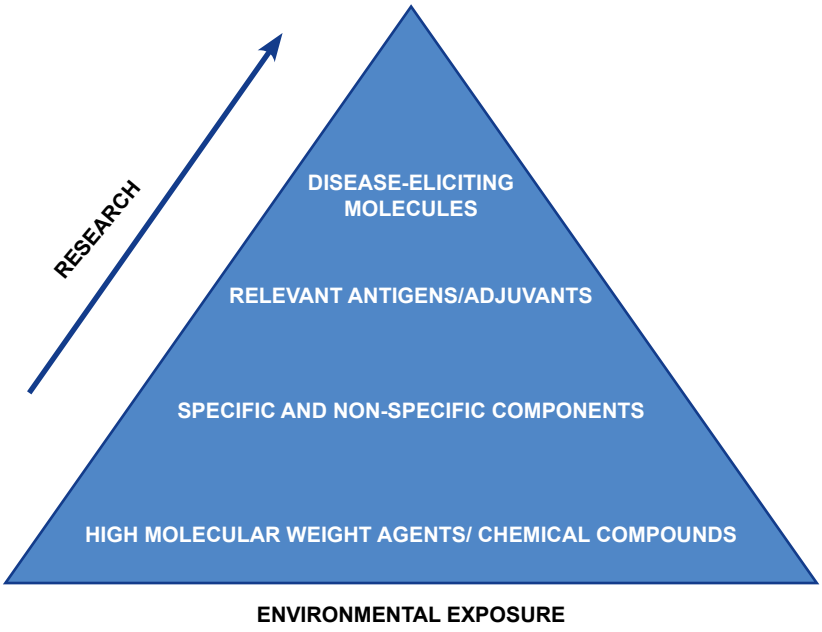

Figure 1 Source of exposure (complex organic dusts or chemicals) contains specific and non-specific components, relevant antigens or haptens and possible adjuvants (cofactors), as well as the true disease-eliciting molecules.

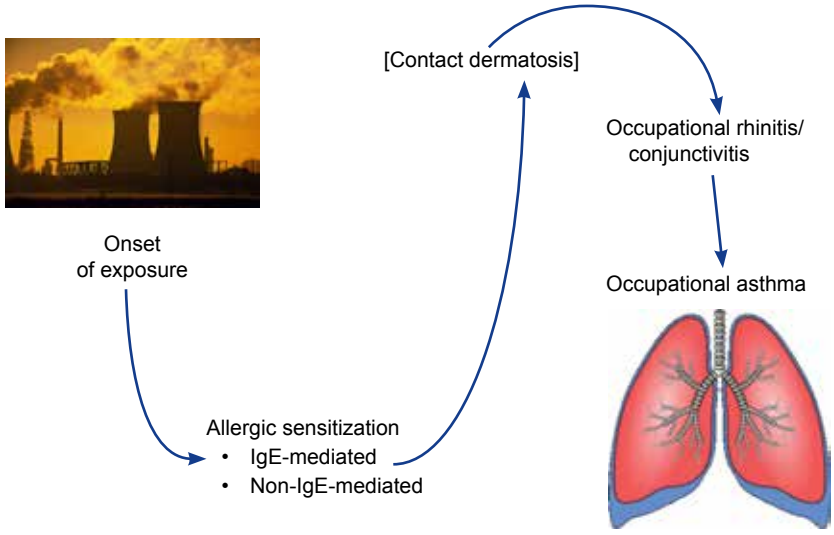

Figure 2 The theoretical model of the natural history of allergic occupational asthma considers that exposed workers first develop immunological reactivity and subsequent to this, symptoms related to a specific organ (skin, naso-conjunctival, respiratory). Cutaneous manifestations may be present or not. This sequence can be termed the 'occupational allergic march'.

with or without systemic manifestations. The disease is a diffuse, predominantly mononuclear inflammation of the lung parenchyma, particularly the terminal bronchioles, interstitium, and alveoli. There is a wide variety of agents that can cause the disease, most of which are present in the workplace. Pathogenic mechanisms of OA and HP are summarized in Figure 4.

Occupational allergic contact dermatitis is one of the most common occupational diseases. Making a timely and accurate diagnosis is important to improving the outcome. Taking a work history and patch testing are essential elements in the diagnostic process.

The appropriate treatment of occupational allergic disorders remains early removal from exposure to the causative agent, in addition to providing conventional allergy treatment.

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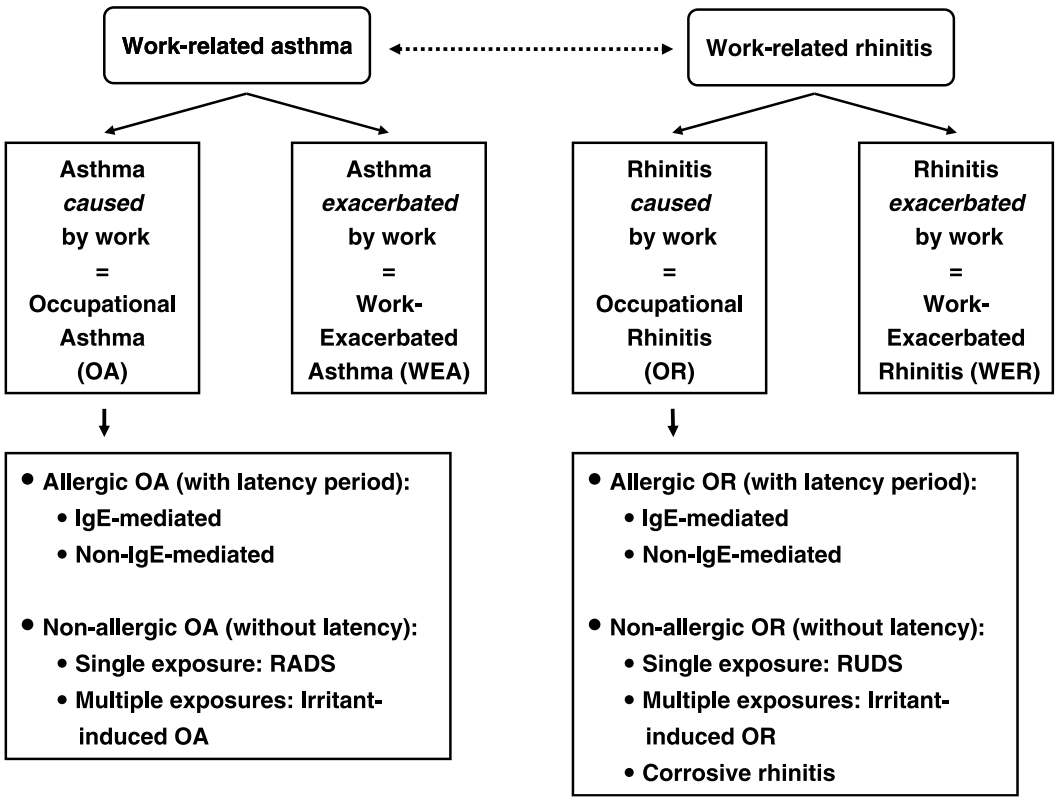


Figure 3 Classification of work-related asthma and work-related rhinitis. (*Reproduced with permission from Moscato G, Vandenplas O, Gerth Van Wijk R,et al. Occupational rhinitis. Allergy 2008;63:969-980, with permission from Willey Blackwell.*)

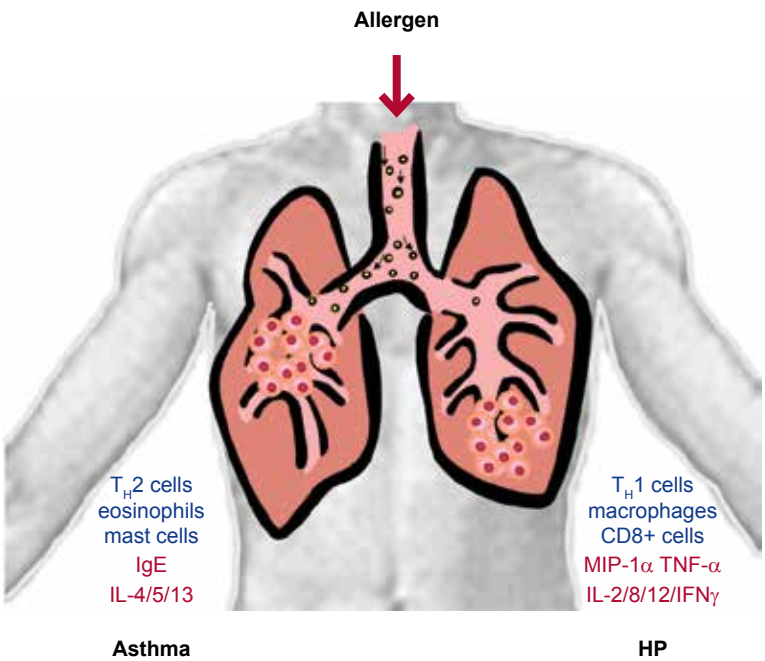
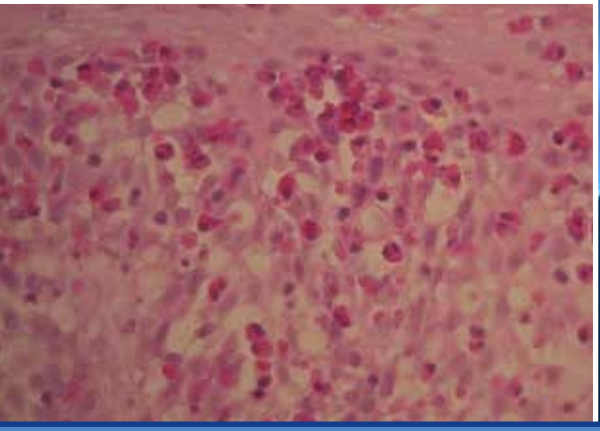


Figure 4 Inhaled allergens can give rise to either asthma or hypersensitivity pneumonitis (HP). Asthma is considered to be a Th2 disease, whereas the pathogenesis of HP is much more complex, with significant participation of delayed hypersensitivity, Th1 cytokines and CD8+ cells.

Section E



OTHER HYPERSENSITIVITY DISEASES

* Eosinophilic esophagitis
* Food protein-induced enterocolitis syndrome
* Reactions to food and drug additives
* Adverse reactions to vaccines for infectious diseases
* Allergic bronchopulmonary aspergillosis
* Hypersensivity pneumonitis
* Mastocytosis
* Hypersensitivity vasculitis

1 EOSINOPHILIC ESOPHAGITIS

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KEY MESSAGES

- Dysphagia for solids is a red flag sign requiring a gastro-eosophageal endoscopy
- Eosinophilc esophagitis (EoE) is a clinicopathological entity diagnostically based on symptoms and eosinophil-predominant inflammation of the esophageal mucosa
- Patients with active EoE have to be treated in order to prevent food impactions and esophageal remodeling
- Drugs (topically steroids), diet and dilation are the currently available treatment modalities

HISTORY

The esophagus is a simple tubular organ, responsible for the transport of food from the oral cavity to the stomach. Originally no striking absorptive or immunologic functions were attributed to this organ. In the mid-1990s, two case series described patients suffering from dysphagia accompanied by a prominent eosinophilic infiltration of the esophagus. Eosinophilic esophagitis (EoE) was recognized as its own entity in the medical literature.

MOLECULAR AND CLINICAL CHARACTERISTICS

EoE represents a Th2-type inflammatory disease with IL-5, IL-13 and eotaxin as key mediators and eosinophils, T cells and basophils as critical cells involved. Remodeling of the esophagus is a hallmark of EoE, leading to esophageal dysfunction and bolus impaction. Familial occurrence, an inflammation-dependent genetic signature together with a genetic abnormality in the eotaxin 3 genes underscore the influence of genetics in this disease.

EoE may affect individuals at any age, though the clinical presentation is highly age-dependent. Whereas children show a wide spectrum of symptoms, including chest pain, feeding problems and failure to thrive, adults present with a rather narrow spectrum, specifically, dysphagia for solids up to food impaction.

There is a significant allergic bias in the EoE population, with more than 70% of patients having concurrent allergic rhinitis, asthma, eczema and/or a history of atopy. Of note, in children, EoE seems to be primarily a food antigen driven disease, whereas in adults, mainly aeroallergen sensitization has been observed.

ENDOSCOPICAL AND HISTOLOGICAL FEATURES

Endoscopy reveals some typical signs, such as edema with loss of vascular pattern, longitudinal furrows and white exudates in the acute inflammatory stage (Figure 1), and strictures and rings, leading to a rigid and narrow esophagus in the fibrotic stage (Figure 2).

Histopathologic key feature of EoE is a characteristic prominent eosinophil infiltration (Figure 3), refractory to treatment with proton-pomp inhibitors.

TREATMENT

Treatment modalities for EoE include the 3D's: Drugs, mainly topical corticosteroids and biologic agents, Diet, and Dilation. Due to their convincing efficacy with response rates of approximately 70% swallowed topical corticosteroids are considered as first line drugs, whereas biologicals or immunosuppressant's are used only for refractory disease.

Figure 1 Endoscopic picture from a patient with active EoE, showing a typical combination of several inflammatory signs, in particular white exudates, longitudinal furrows and edema.

Figure 2 Endoscopic picture from a patient with longstanding EoE, showing a minimal inflamed mucosa but distinct fibrotic rings.

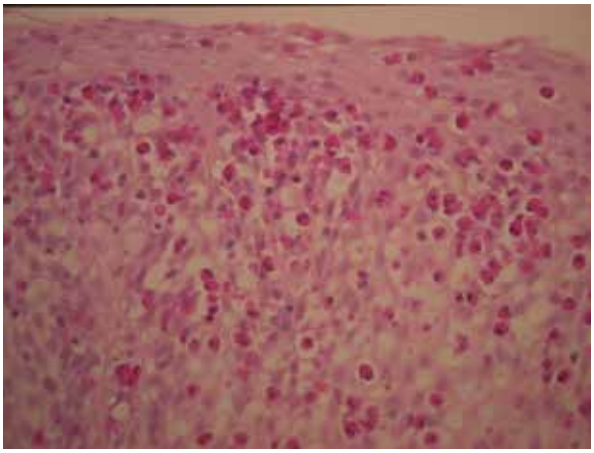

Figure 3 Esophageal mucosa from a patient with active EoE showing a marked infiltration of the epithelium with eosinophils. (HE staining, original magnification 400x.)

Among dietary approaches, elemental diet avoiding any proteins is the most powerful modality, but requires usually a nasogastric feeding tube. Dilation is efficient in relieving symptoms, but does not influence the underlying inflammation and is therefore mainly used as second line modality in patients having strictures refractory to medical or dietary treatment.

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2 FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

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KEY MESSAGES

- Food protein-induced enterocolitis syndrome (FPIES) is classified as a non-IgE-mediated food allergy
- FPIES-diagnosis is frequently delayed due to absence of allergic cutaneous and respiratory symptoms and lack of biomarkers
- Supervised oral food challenge is necessary for monitoring FPIES resolution
- FPIES is usually outgrown by age 3-5 years; IgE-sensitization may develop in a subset of subjects and seems to be associated with a more protracted course

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy with typical onset in infancy. FPIES is characterized by repetitive vomiting that begins approximately 2 hours following food ingestion, and often progresses to lethargy, diarrhea and additional signs and symptoms suggesting a systemic reaction distinct from IgE-mediated anaphylaxis (e.g., lacking urticaria or obstructive respiratory symptoms). In severe cases (about 15%) hypothermia, methemoglobinemia, acidemia, and or hypotension/shock may develop. Laboratory findings typically reveal elevated white blood cells with neutrophilia, and may include thrombocytosis. In young infants, the presentation often mimics sepsis.

Manifestations of FPIES vary depending on the exposure to the offending food and may be acute of not of chronic (Table 1). The appearance of acute symptoms following a period of food avoidance is the feature that distinguishes FPIES from other gastrointestinal food allergy disorders, such as enteropathy, eosinophilic gastroenteritis, or celiac disease.

In the majority of children (>60%) FPIES is caused by a single food. The most common single food allergens in FPIES are cow's milk (CM), soy and rice. Solid foods including cereal proteins such as rice and oat, egg, fish, vegetables, and poultry have been reported in children, whereas shellfish and mollusks have been reported in adults.

The prevalence of FPIES is unknown. The only population-based birth cohort study in Israel reported CM-FPIES in 0.34% of 13,019 infants, compared to 0.5% of IgE-mediated CM-allergy diagnosed in the first year of life.

The pathophysiology of FPIES remains poorly defined. Ingestion of food allergens may cause local inflammation leading to increased intestinal permeability and fluid shift. Antigen-specific T cells and imbalance between TGF-β and IFN-γ that affects intestinal barrier permeability may play a role. Systemic food-specific IgE antibodies are typically absent in FPIES.

Diagnosis of FPIES relies on recognition of a constellation of symptoms and an oral food challenge (OFC) (Table 1 and 2). In infants with classic symptoms, recurrent reactions, especially associated with hypotension, and who are well when the food is eliminated, OFC may not be necessary for an initial diagnosis. OFCs are necessary for evaluating for FPIES resolution. Management relies on food elimination, treatment of acute re-

TABLE 1

Characteristics of acute and chronic FPIES

	Acute FPIES (Food ingested intermittently)	Chronic FPIES* (Food ingested on a regular basis, e.g. CM or soy infant formula)
Clinical features	**Always**: Vomiting: onset usually in 2 hours [30 min-4 hours], repetitive (up to 10-20 times), may be severe and projectile; **Almost always**: pallor, lethargy; **Other variable features**: dehydration, diarrhea (onset usually within 12 h), bloody diarrhea, abdominal distention, hypotension, hypothermia	Intermittent vomiting, diarrhea, lethargy, weight loss, failure to thrive, weight gain <10 g/day, bloody diarrhea, abdominal distention, Dehydration
	Symptoms usually resolve within 6-12 hours	Symptoms usually resolve within several days
Laboratory features	Elevated white blood count (WBC) with left shift, thrombocytosis, methemoglobulinemia, acidosis	Elevated WBC with left shift and eosinophilia, anemia, hypoalbuminemia, low total protein, acidosis, methemoglobulinemia
	Stool: Blood, mucous, sheets of leukocytes and eosinophils, and increased carbohydrate content	Stool: Occult blood, polymorphonuclear neutrophils, eosinophils, Charcot-Leyden crystals and reducing substances
	Intramural gas may be seen on abdominal x-rays	Air-fluid levels, non-specific narrowing and thumb-printing of the rectum and sigmoid, and thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid
	Endoscopy: friable mucosa with rectal ulceration and bleeding	Endoscopy: friable mucosa with rectal ulceration and bleeding
Food triggers	Any food; most common CM, soy**, and rice	CM and soy
Age of onset	Any; most cases start under 1 year but fish and shellfish FPIES may start at any age	Within 1st year of life
Diagnosis	Based on typical clinical manifestations; oral food challenge (OFC) may be not necessary in infants with repeated reactions, especially with hypotension, who are well when food is eliminated from the diet. Skin prick tests and serum specific IgE antibodies to offending food(s) usually negative	Suspected on the basis of clinical manifestations, confirmed by a supervised OFC following a period of dietary food elimination. Skin prick tests and serum specific IgE antibodies to offending food(s) usually negative
Differential diagnosis	Sepsis; Gastrointestinal infections; Anaphylaxis; Ileus, intussusception; Necrotizing enterocolitis (NEC);	Eosinophilic gastro-enteropathies, Food protein-induced enteropathy, Allergic proctocolitis; Celiac disease; Inborn errors of metabolism; Congenital methemoglobinemia; Cardiovascular or neurologic disorders; Gastroesophageal reflux disease
Management	Strict food elimination, may require nutritional consultation; breast-feeding is usually well tolerated; Fluid resuscitation; Single dose of methylprednisolone for more severe reactions; Ondansetron may be considered for severe emesis; Bicarbonate for acidosis; Methylene blue for methemoglobulinemia; Food reintroduction can be attempted within several months following the most recent reaction; in one approach, OFC is delayed for 12-18 months following a reaction***	Strict food elimination, may require nutritional consultation; breast-feeding is usually well tolerated Fluid resuscitation Bicarbonate for acidosis Methylene blue for methemoglobulinemia Temporary bowel rest with intravenous feeding
Age of resolution	Variable, population-dependent; CM-FPIES resolution by age 3 years ranges from 30% in referral population to 100% in unselected populations	

** Chronic FPIES has become uncommon, presumably due to the wide availability of the hypoallergenic infant formulas that are being used empirically.*

*** In the US the reactivity to both CM and soy, as demonstrated in single center retrospective case series, has been noted to range between 30-50%. However, outside the US, a far smaller percentage of children suffer concomitant FPIES to CM and soy.*

****This is an empiric approach; controlled studies are necessary to develop evidence-based guidelines for FPIES management.*

TABLE 2

Characteristics of acute and chronic FPIES	
Basic requirements	Physician supervision Secure peripheral intravenous access in patients with history of severe FPIES reactions or those with anticipated difficult access, e.g., infants Immediate availability of fluid resuscitation
Baseline laboratory tests	Peripheral neutrophil count [complete blood count with differential]
Challenge administration	Food amount is calculated as 0.06 - 0.6 g/kg body weight in three equal doses, generally not to exceed total 3 g protein or 10 g of total food (100 ml of liquid) for an initial feeding* Food is divided in 3 equal portions and fed over 30 minutes if food-specific IgE is negative; modification of the challenge and more incremental dosing is used for patients with positive food-specific IgE
Treatment of the reaction	Fluid resuscitation: 20 ml/kg IV boluses of normal saline Steroids: methylprednisolone 1 mg/kg IV, max 60 to 80 mg The role of intravenous ondansetron in the management of acute FPIES reactions is being currently evaluated Epinephrine and antihistamines are not effective in FPIES
Post-challenge laboratory tests	Peripheral neutrophil count [completed blood count with differential]: at 6 hours if the patient reacted or at discharge if the patients tolerated the challenge If stool sample available: test for occult blood and stool smear for leukocytes
Post-challenge observation	About 6 hours after the resolution of symptoms or 4 hours after feeding in case of no symptoms
Criteria for challenge positivity**	1. Emesis (onset 0.5-4 hours, usually 2 hours) 2. Diarrhea (onset 2-10 hours, mean 5 hours) 3. Elevated neutrophil count (>3500 cells/mL, peaks at 6 hours) 4. Fecal leukocytes 5. Fecal eosinophils

**If no reaction in 2-3 hours, administer an age appropriate serving of the food followed by several hours of observation;*
*** Challenge is considered positive if 3 of 5 criteria are met and equivocal if 2 of 5 criteria are met.*

actions and periodic OFC, as outlined in Figure 1.

Resolution of FPIES varies widely among reports from different countries. The Israeli birth cohort showed 90% resolution of CM-FPIES by age 3 years, whereas experience from allergy referral populations in the U.S. showed 60% resolution by age 3 years. Sicherer et al.observed that children with detectable food-specific IgE tend to have a more protracted course and are at risk of developing IgE-mediated immediate-type symptoms. Therefore, including SPT and/or measurement of serum food-specific IgE levels in the initial as well as follow-up evaluations is prudent to determine timing and the type of oral food challenges.

Further research should focus on the pathophysiology and natural history of FPIES, as well as the unique diagnostic tools for initial diagnosis and monitoring of tolerance development.

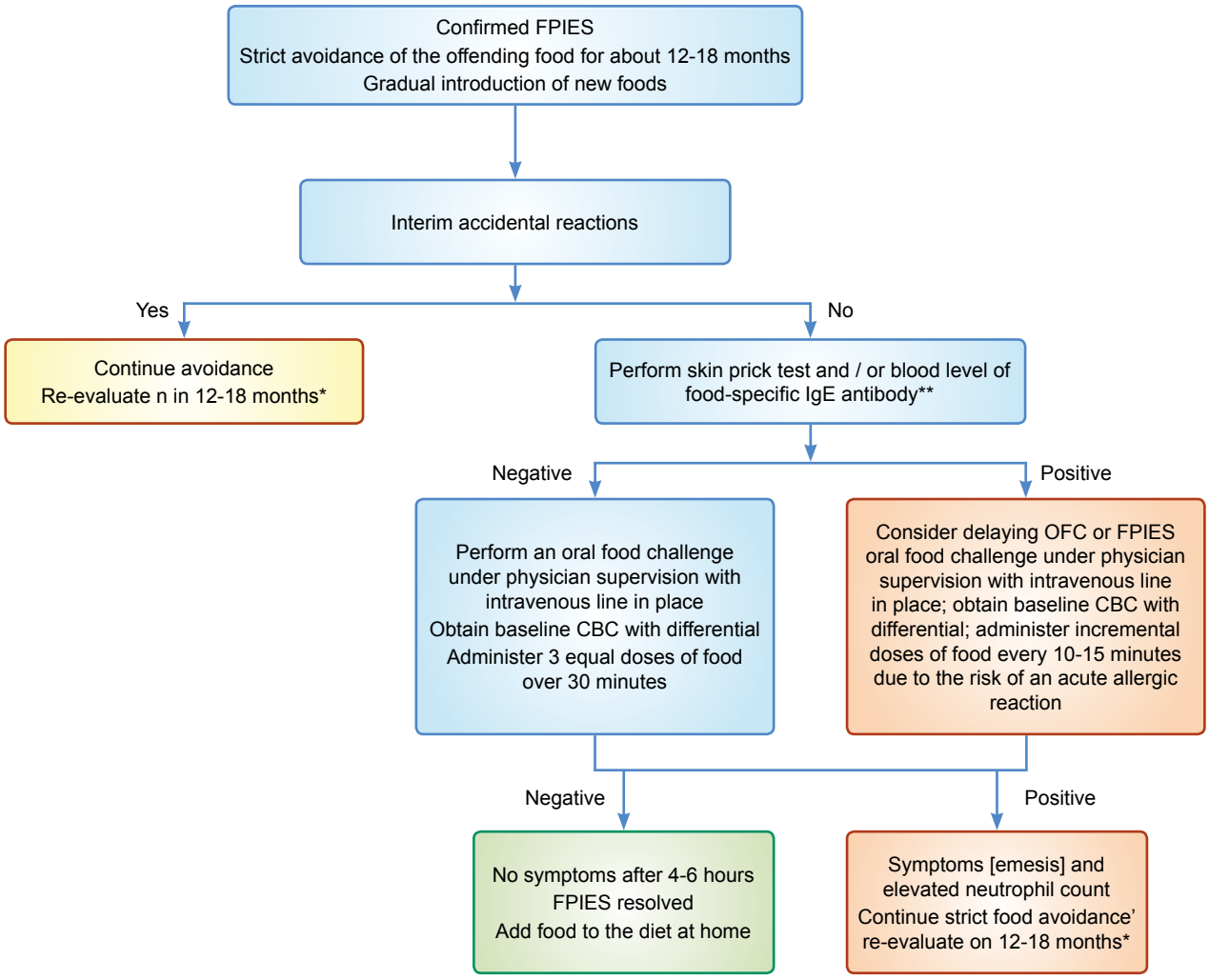

Figure 1 Empiric approach to FPIES management. (*The timing of the follow up food challenges is arbitrary; food challenge may be performed earlier or deferred for a longer time, depending on individual circumstances. ** A subset of patients may develop IgE-sensitization and progress to immediate symptoms, requiring modification of the oral food challenge procedure)

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3 REACTIONS TO FOOD AND DRUG ADDITIVES

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KEY MESSAGES

- The self reported rate of food intolerance is 6-10 higher than proven by double-blind placebo-controlled food challenge
- The frequency of non-IgE dependent food or drug hypersensitivity reactions in the general population is 1-2%
- Food and drug additives (e.g. colorants, preservatives) can trigger immediate hypersensitivity reactions
- Clinical manifestations include primarily urticaria, asthma and eczema
- A possible association between the high intake of food additives and hyperreactivity is highly controversial

Food or drug intolerance describes any reaction to food or drugs ranging from food toxicities to reproducible symptoms consistent with an IgE-mediated reaction to non-reproducible symptoms such as diarrhoea or headache.

Reported triggers include naturally derived and artificial food or drug additives including colourings, flavourings and preservatives, but also other ingredients such as lactose and artificial sweeteners. Patient-reported rates of food intolerance range from 7 to over 20%. The reported rate is 6 to 10 times greater than the prevalence determined through double-blind placebo-controlled food challenge (DBPCFC). Approximately 1 to 2% of the population may have non-allergic food hypersensitivity. Drug intolerance due to additives has been rarely reported in the literature, but there are no controlled prospective studies on its prevalence.

Immune reactions are usually mediated through non-IgE mediated mast cell degranulation (Figure 1). Non-immune reactions might be derived due to:

1. Pharmacological effects: Food rich in vasoactive amines (e.g. histamine) can induce symptoms, either by direct action or by causing the release of histamine in vivo.
2. Enzyme deficiencies: Excessive consumption of fruit juices (fructose) or sugar-free foods (sorbitol) can promote anosmotic diarrhoea which may mistakenly be diagnosed as food intolerance.

Food or drug additives are used to resolve or improve the texture and taste of the related products. Tartrazine, the most studied additive is an artificial food colorant reported to provoke urticaria, eczema, vasculitis, asthma and even anaphylaxis. Sulfite is also used to preserve food and drugs. It can cause bronchoconstriction in children and in adults with asthma. Benzoic acid is a preservative in drinks and pickled foods and is also frequently found in liquid formulations of common medicines including non-steroidal antiinflammatory drugs. Benzoate can trigger urticaria, atopic eczema or rhinitis. Monosodium glutamate is obtained synthetically and is used as a flavour enhancer in many foods. It has been reported in a set of symptoms known as the "Chinese restaurant syndrome", which includes flushing, headache and palpitations. Salicylates involvement is controversial and depends on their acetylation status. Acetylated salicylates can trigger asthma, but also other symptoms of an allergic reaction.

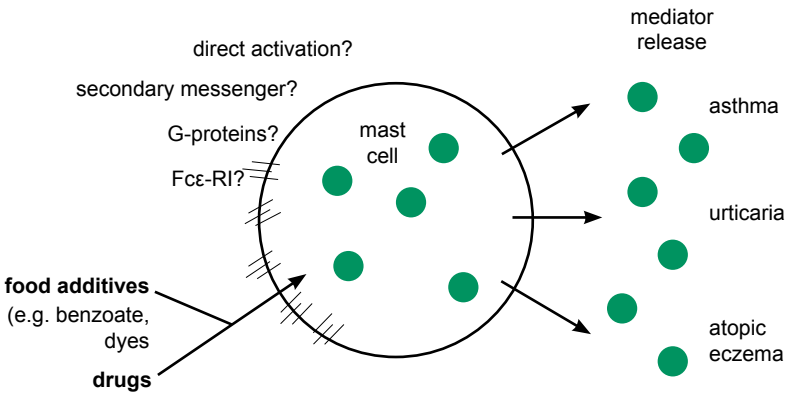

Figure 1 Possible mechanisms of additive triggered mast cell activation.

TABLE 1

Examples of food or drug additives triggering non-IgE hypersensivity reactions	
Colourings	Colourings may trigger symptoms in chronic urticaria and atopic dermatitis. Tartrazine may trigger bronchospasm in a limited number of individuals with asthma.
Preservatives	Benzoates & acetylated salicylates (aspirin) may be a trigger in chronic urticaria and atopic dermatitis. Sulfites can trigger asthma, probably through release of sulphur dioxide.
Artificial Sweeteners	The few case reports of urticaria to aspartame were not replicated by most studies using DBPC challenges.
Flavouring/ enhancers	The hypothesis that monosodium glutamate causes 'chinese restaurant syndrome' was not replicated with DBPC challenges.
Antioxidants	The few case reports of urticaria to BHA/BHT were not replicated with DBPC challenges.

A summary of evidence for food additives and colourings as a cause of non-allergic food hypersensitivities is depicted in table 1.

An association between the high intake of food additives and hyperactivity is highly controversial. The Southampton Study published in 2007 reported a small, but statistically significant increase in hyperactivity levels with additives compared to placebo, but the effect was not consisted across both age groups and the overall effect did not reach statistical significance. In summary, there is not enough consistent data to confirm a role of food colourings in hyperactive behaviours.

The standard diagnostic procedure in patients with suspected non-IgE-mediated food hypersensitivity to additives is an elimination diet over 4 weeks followed by DBPC challenges using the additives in standard concentrations. Such provocation tests are also applicable if a drug additive hypersensitivity reaction is suspected. In the absence of a positive DBPC challenge the elimination diet should be stopped.

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4 ADVERSE REACTIONS TO VACCINES FOR INFECTIOUS DISEASES

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Adverse events after vaccine administration are commonly reported, constituting a major problem in clinical practice. A correct management of these reactions is of major importance, as they are clearly associated with a decreased vaccination rate in the general population.

KEY MESSAGES

- Adverse events after vaccine administration are commonly reported and correct diagnosis and management of potential severe reactions is essential to avoid a decreased vaccination rate
- Local reactions have not been associated with a higher rate of systemic reactions and an allergic workup is usually not required
- The most common systemic reactions include maculopapular or delayed urticarial skin rashes. These reactions do not contraindicate further vaccine administration
- Systematic approaches have been proposed to optimally manage patients with a suspicion of vaccine hypersensitivity

LOCAL REACTIONS TO VACCINES

Local reactions are the most frequent adverse event after vaccine administration and patients experiencing this type of reactions are often falsely labeled as allergic. However, local reactions have not been associated with a higher rate of systemic reactions and an allergic workup is usually not required.

In patients developing large local reactions (suspicion of Arthus reaction) measurement of serum vaccine-specific antibodies can be useful for the decision to withhold additional dose. In patients developing eczema or persistent nodules, patch tests can be performed to diagnose delayed hypersensitivity to vaccine preservative or adjuvant. However, a positive patch test should not be considered as a contraindication for booster injection.

SYSTEMIC REACTIONS TO VACCINES

The most common systemic reactions include maculopapular or delayed urticarial skin rashes. These reactions do not contraindicate further vaccine administration, as they are believed to result from a non-specific activation of the immune system.

Real IgE-mediated allergies to vaccine are extremely rare, but their identification is important due to the potential life-threatening risk. Systematic approaches have been proposed to optimally manage patients with a suspicion of vaccine hypersensitivity (Figure 1).

- In patients with a history of allergy to one of the vaccine constituents (i.e. egg, gelatin, yeast, formaldehyde, antibiotics and latex), who have not received the vaccine before, a complete allergic work-up is recommended (i.e. skin tests, specific IgE measurement and/or a provocation test) to confirm an allergy. If this is the case, skin test with the vaccine itself should be performed. If positive, the vaccine can still be administered using adapted protocols. Regarding administration of influenza vaccine in patients with severe egg allergy, it has been shown that the vaccine can be

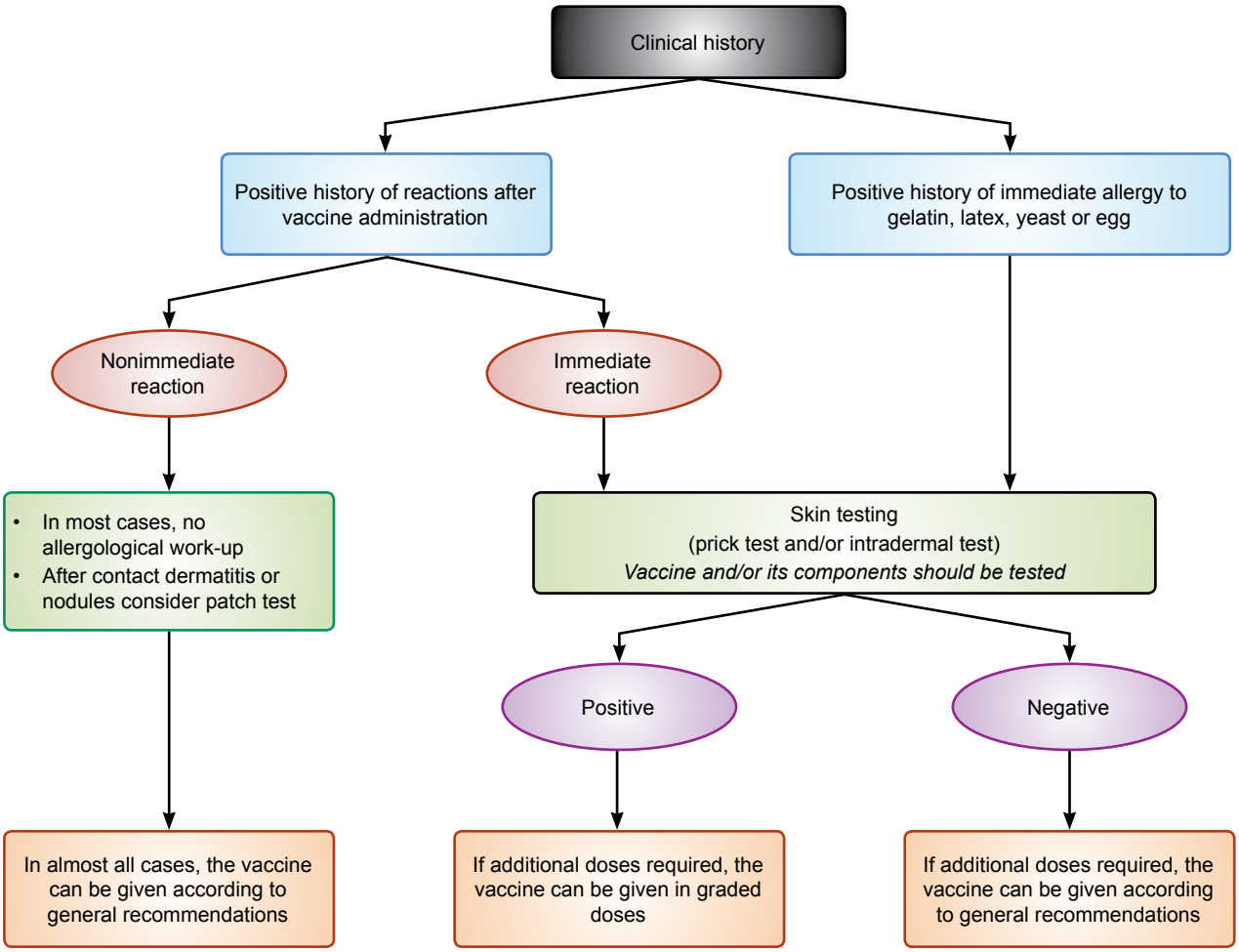

Figure 1 Management of patients with suspected hypersensitivity to a vaccine and of patients with known allergy to a vaccine component. (*Reproduced with permission from Caubet JC, Rudzeviciene O, Gomes E, et al. Managing a child with a possible allergy to vaccine, Pediatric Allergy Immunology 2013;Oct 16. doi: 10.1111/pai.12132. [Epub ahead of print] with permission from Willey Blackwell.*)

administered safely with some precautions. Skin test to the influenza vaccine before vaccination is no longer recommended.

- In patients with a history of systemic reactions to vaccine, the allergic workup should include testing of the vaccine itself as well as its components. In case of a positive test to one of the components, one can consider a vaccine not containing that component, if available. If the patient is positive to the vaccine, a risk-benefit assessment should be performed; the physician should determine whether subsequent doses of the suspected vaccine are necessary. Measurement of vaccines antibodies to determine whether they are at protective levels helps determining whether booster injection can be withheld.

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5 ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

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KEY MESSAGES

- Allergic bronchopulmonary mycoses are rare pulmonary type I and III hypersensitivity reactions, most commonly directed against *Aspergillus fumigatus*, but many other fungi can serve as antigen source
- ABPA occurs on the background of either allergic asthma or cystic fibrosis
- Symptoms include wheezing, cough, malaise, fever, chest pain and the production of copious amounts of purulent sputum containing fungal hyphae
- Radiological features of ABPA are central bronchiectasis and fleeting pulmonary infiltrates. Considerable airflow obstruction, often combined with loss of lung volume is also present
- The diagnosis of ABPA is difficult and requires a multidisciplinary approach. Major and minor criteria are described
- Treatment aims to prevent exacerbations to avoid progressive and eventually fatal loss of lung tissue. Glucocorticosteroids and antimycotics are the mainstay of treatment. Allergen avoidance is crucial to prevent progression

Allergic bronchopulmonary mycoses are rare pulmonary hypersensitivity reaction , most commonly directed against *Aspergillus fumigatus* (Allergic Bronchopulmonary Aspergillosis - ABPA). Many other fungi can also serve as antigen source, hence the term allergic bronchopulmonary mycosis.

ABPA occurs on the background of either allergic asthma or cystic fibrosis. The disease occurs mainly sporadic, but familial clustering has been reported. The pathogenesis of ABPA involves complex local as well as systemic hypersensitivity reactions to fungal antigens from fungal mycelia, which grow in the bronchial lumen, where they cause local inflammation and subsequent tissue destruction resulting in central bronchiectasis. In addition to a marked cellular inflammation with eosinophils and neutrophils there is a humoral component involving polyclonal IgE-, IgG- and IgA production. Consequently, the complex immunopathogenesis of ABPA appears to involve type I as well as type III immune reactions. Comorbidities such as allergic rhinitis are frequent.

Symptoms include wheezing, cough, malaise, fever, chest pain and the production of copious amounts of purulent sputum, which often contains fungal hyphae. Radiological features of ABPA are central bronchiectasis and fleeting pulmonary infiltrates, which do not respond to antibiotic therapy but to systemic corticosteroids instead. Most patients have a considerable airflow obstruction, often combined with loss of lung volume due to pulmonary destruction by infiltrates and bronchiectasis and require high dose bronchodilator therapy in addition to anti-inflammatory glucocorticosteroids.

The diagnosis of ABPA (Table 1) is difficult and there is a considerable lag time between first occurrence of symptoms and diagnosis, often lasting many years. Recombinant *Aspergillus* antigens such as rASP f4 and rASP f6 have been implicated to be rather specifically elevated in ABPA. IgE levels in

TABLE 1

Diagnostic criteria for the diagnosis of ABPA	
Major criteria	• asthma or cystic fibrosis • central bronchiectasis (HRCT) • positive skin tests to fungal allergens, most frequently to *A. fumigatus* • elevated IgE levels (>400kU/L) • elevated specific IgE- or IgG-concentrations against *Aspergillus*-specific antigens
Minor criteria	• radiologic inflitrates • precipitating antibodies against *A. fumigatus* (or other fungi) • peripheral blood eosinophilia of 1000/ml • tenacious, brown-coloured sputum plugs • positive *A. fumigatus* cultures from sputum • late reaction to *A. fumigatus* skin prick tests

TABLE 2

Stages for ABPA

Criteria	Stages					
	Seropositive ABPA	Stage I (acute)	Stage II (Remission)	Stage III (Exacerbation)	Stage IV (Asthma)	Stage V (Fibrosis)
Asthma	+	+	+	+	+	+
Radiologic infiltrates/ radiologic changes	+/-	(+)	+/-	+	+/-	+
Cutaneous reaction to *A. fumigatus*	++	+	+	+	+	+
Elevated IgE levels	++	+++	+/-	+++	+/-	+/-
Precipitating antibodies to *A. fumigatus*	+	+	+/-	+	+/-	+/-
Peripheral blood esinophilia	+/-	+	-	+	+/-	-
Central/proximal bronchiectasis	-	+	+	+	+	+
Elevated *A. fumigatus*-specific IGe and IgG	+	+	+/-	+	+/-	+/-

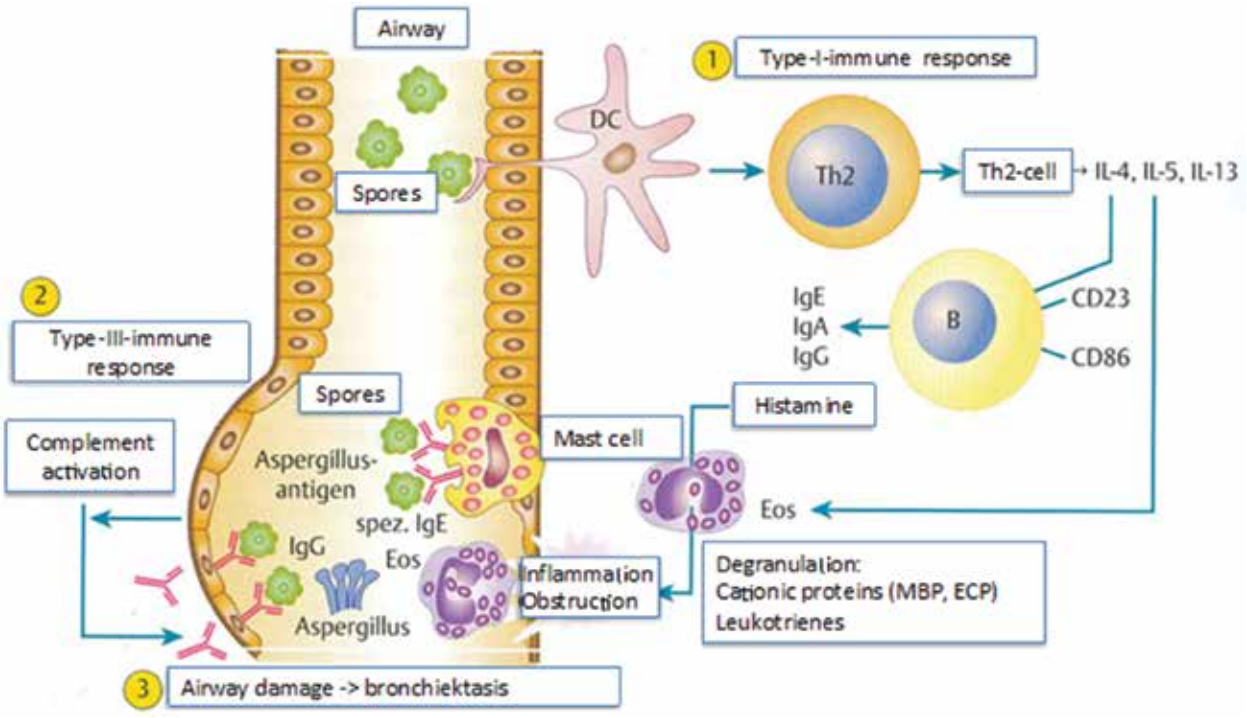

Figure 1 Immunopathogenesis of ABPA. (*Modified from Virchow J.C. Allergische bronchopulmonae Aspergillose. In: Heppt W, Bachert C, eds. Praktische Allergologie, Thieme, Stuttgart 2nd ed, 2011; pages 57-64.*)

ABPA can serve as markers for impending exacerbations. ABPA has been classified in different stages (table 2)

Treatment of ABPA requires considerable experience and a specialist environment. Treatment aims are to prevent exacerbations by reducing endo-bronchial inflammation to avoid progressive and eventually fatal loss of lung tissue. Glucocorticosteroids and antimycotics, both with a considerable potential for side-effects, are the central pillars of treatment. There are occasional case reports of successful treatment of ABPA with Omalizumab. Many patients in stage IV require maintenance treatment with systemic corticosteroids.

Allergen avoidance at home or workplace are crucial to prevent progression. Treatment in high altitude such as Davos, Switzerland improves symptoms and reduces inflammation, most likely due to the low antigen content in these special environments.

Prognosis is highly dependent on an early diagnosis and appropriate treatment. Therefore, pneumologic experience and a comprehensive clinical, immunologic and radiologic workup are necessary to identify patients with this debilitating disease. Treatment should be directed at the early identification of exacerbations to avoid the development of fatal pulmonary destruction.

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6 HYPERSENSIVITY PNEUMONITIS

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KEY MESSAGES

- Hypersensitivity pneumonitis (HP) is an interstitial lung disease due to a combined type III and IV reaction with a granulomatous inflammation, caused by T lymphocytes in a Th1/Th17 milieu, chaperoned by a deficient suppressor function of T regulatory cells. Skewing toward a Th2 phenotype is reported for chronic HP
- Phenotypic expression and severity depends on environmental and/or host genetic and immune co-factors
- The wide spectrum of causative antigens is continuously updated with new sources of airborne organic particles and drug-induced HP
- The diagnosis requires a detailed history, measurement of environmental exposure, pulmonary function tests, imaging, detection of serum specific antibodies, broncho-alveolar lavage, antigen-induced lymphocyte proliferation, environmental or laboratory-controlled inhalation challenge and lung biopsy
- Complete antigen avoidance is the best therapeutic measure, although very difficult to achieve in some cases. Systemic steroids are of value for subacute and chronic forms of HP, but do not influence long-term outcome. Manipulation of the immune response holds future promise

Hypersensitivity pneumonitis (HP) is an interstitial lung disease due to a combined type III and IV reaction with a granulomatous inflammation. The current view is that HP is caused by cytotoxic delayed hypersensitivity lymphocytes, in a Th1/Th17 milieu (Figure 1). Both TLRs 2 and 9 contribute to the Th17 response and neutrophil recruitment. Additional mediators and pattern recognition receptors are involved in granuloma formation. Loss of T-regulatory cells (Tregs) control over the immune response is essential for the impaired immune tolerance in HP. The mechanisms of progression to a chronic form remain unclear. For chronic HP a skewing toward a Th2 phenotype facilitated by group 2 innate lymphoid cells was described.

Although many individuals are exposed to environmental antigens known to induce HP only 5-15% develop the disease. The phenotypic expression of the disease depends on environmental co-factors, such as viruses and/or host genetic and immune co-factors, which also promote considerable variability in disease severity and response to treatment.

HP can occur in an occupational setting or after home exposure, following inhalation of organic antigens (mammalian and avian proteins, fungi, bacteria), low-molecular-weight chemicals or Mycobacterium avium-intracellulare complex organisms. As a non-inhalant variant HP can appear as a manifestation of drug-induced lung disease. Most recent reported drugs inducing HP are immune modulators used to treat neoplastic and connective tissue diseases or transplant recipients. New sources of airborne organic particles are continually being recognized, such as the thrombone player, Chacinero's lung, HP associated with catechin-rich green tea extracts, use of ultra-

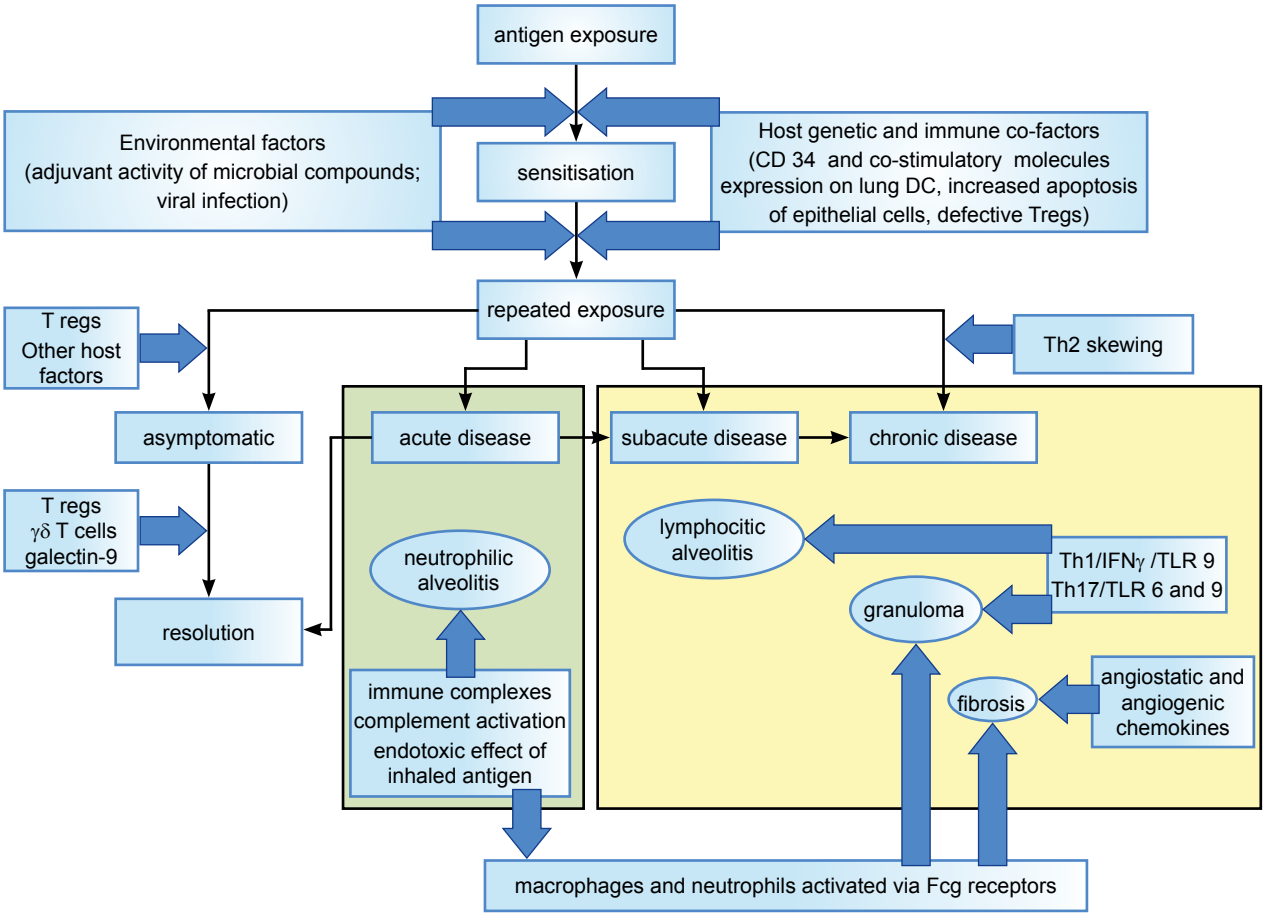

Figure 1 Pathogenenic mechanisms in hypersensivity pneumonitis. (*From Agache I, Rogozea L. Management of hypersensivity pneumonitis. Clin Transl Allergy. 2013;3:5; Reprinted with permission under the Creative Common Attribution License or equivalent.*)

sonic misting fountains at home, Shiitake mushroom spores, mosquito-coil smoke, medium-density fiberboard or cash handling.

There is no single diagnostic single procedure or biomarker to confirm the diagnosis of HP. The diagnosis requires a detailed and careful history that would include social, environmental, and occupational status, measurement of environmental exposure, pulmonary function tests, imaging, detection of serum specific antibodies, examination of broncho-alveolar lavage fluid (BALF), antigen-induced lymphocyte proliferation, environmental or laboratory-controlled inhalation challenge with the suspected antigen and lung biopsy. A sentinel case should prompt to the identification of exposed subjects, who might develop the disease. Improvement of symptoms away from exposure and/or a rapid response to oral steroids should heighten the awareness of HP.

For monitoring HP activity measurement of alveolar NO following re-exposure and of biomarkers reflecting the lung injury/regeneration cycle such as serum serum Krebs von den Lungen-6 mucin (KL-6) and surfactant protein D are proposed.

Complete antigen avoidance is the essential step in the management of HP. The majority of cases improves or heals, but some evolve to a chronic form probably due to persistence of exposure at an undetectable level in association with genetic and immunologic factors. Systemic corticosteroids are recommended for subacute and chronic forms of HP, although they do not influence long-term outcome. For progressive chronic HP immunosuppressants may be necessary (Figure 2).

Modulation of the immune response holds future promise for treatment. In a HP experimental model CTLA-4Ig promoted a sig-

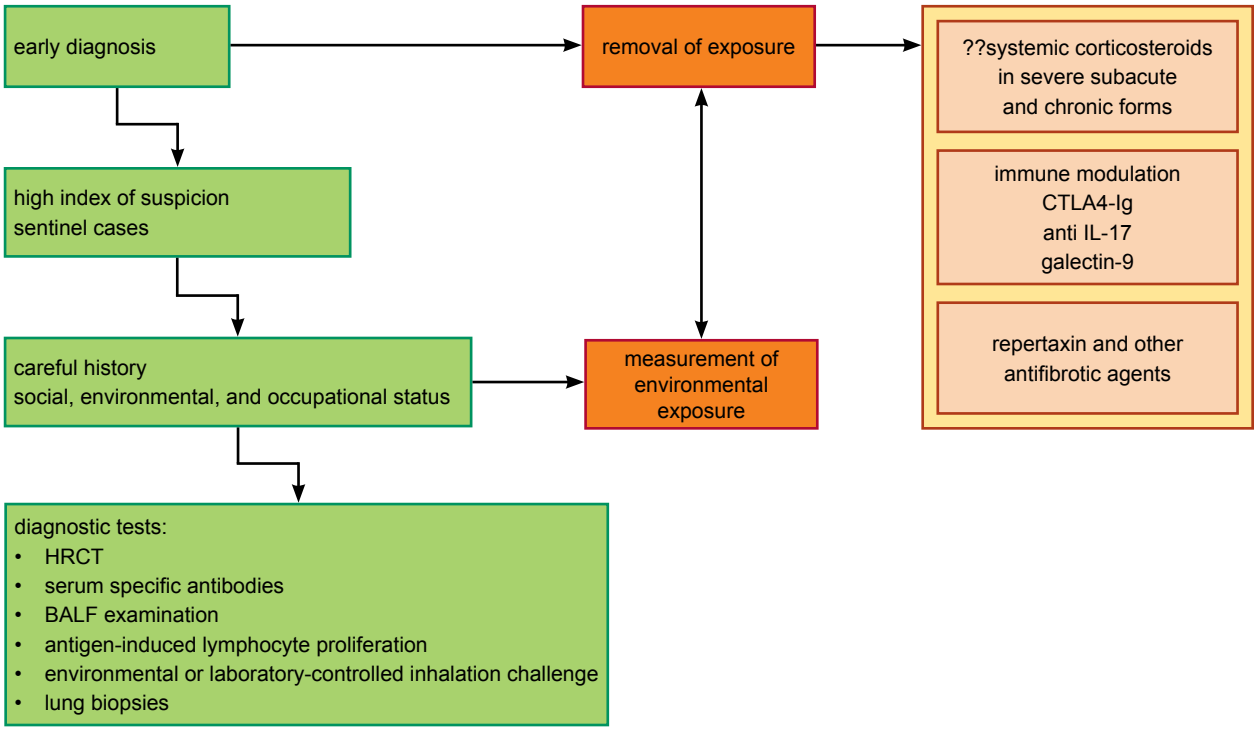

Figure 2 Management of hypersensivity pneumonitis. (*From Agache I, Rogozea L. Management of hypersensivity pneumonitis. Clin Transl Allergy. 2013;3:5; Reprinted with permission under the Creative Common Attribution License or equivalent.*)

nificant decrease in the extent of lung damage and in the number of BALF inflammatory cells, with diminished CD4/CD8 T cell ratio and a significant increase in the lung γδT, NKT cells and Tregs. Other potential targets for immune modulation are T-bet, dendritic cells and adjuvant factors, Tregs and activated cytotoxic T cells (figure 2).

The GAP model, a clinical prediction model based on sex, age, and lung physiology, predicts mortality in chronic HP. Pulmonary hypertension is not rare in chronic HP and significantly impacts survival. The reported prevalence of lung cancer in chronic HP (10.6%) is similar to idiopathic pulmonary fibrosis.

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7 MASTOCYTOSIS

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Mastocytosis is a clonal disorder of the hematopoietic system in which there is a pathological accumulation of mast cells in tissues. In some cases, mastocytosis presents with episodes of mediator release, which are associated with flushing or anaphylaxis. It can affect all age groups. The prevalence is not known. Recent studies have reinforced the role of activating mutations in KIT.

KEY MESSAGES

- Mastocytosis is a clonal disorder of mast cells and thus its diagnosis should follow strict diagnostic criteria
- Episodes of mast cell mediator release may occur, which include flushing and even anaphylaxis
- Cutaneous mastocytosis in children may resolve with time. In adults, cutaneous disease usually persists and is accompanied by systemic disease
- The treatment of mastocytosis is largely symptomatic. Aggressive forms of disease are treated with cytoreductive agents including tyrosine kinase inhibitors and performed in a collaborative effort with a hematologist
- The care of a patient with mastocytosis must include counseling on the consequences of the disease and careful follow-up

DIAGNOSIS AND CLASSIFICATION

The diagnosis of systemic mastocytosis (SM) is established on the basis of a bone marrow biopsy and smear, flow cytometry, mutational analysis of KIT, and serum tryptase (Table1). The classification of variants of mastocytosis is shown in Table 2.

The most frequent form of mastocytosis is indolent systemic mastocytosis (ISM), which tends to follow a benign course. In contrast, aggressive forms of mastocytosis, including SM with an associated hematologic non-mast-cell-lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL), may lead to disability or even death.

CLINICAL FEATURES OF DISEASE

Two-thirds of all cases of mastocytosis present in childhood, with a second peak of onset in the late third to early fourth decade. The disease occurs in both males and females with roughly equal frequency. Cases of mast cell disease diagnosed in childhood often resolve by adulthood, whereas adult-onset mastocytosis usually persists. Although there are cases of familial cutaneous mastocytosis, most patients report no family history. IgE-mediated allergy is not increased.

Clinical symptoms follow patterns of organ system involvement, which includes the skin (Figure 1), gastrointestinal tract, lymph nodes, liver, spleen, and bone marrow. Episodes of flushing and life-threatening episodic hypotension may occur and are sometimes related to alcohol ingestion, insect stings, infection, certain medications, and radio -contrast materials. In patients with aggressive disease, fatigue and musculoskeletal pain are frequent and may be accompanied by weight loss, fever and sweats. Chronic symptoms include headache, decreased attention span, irritability and depression. Abdominal pain is common,

TABLE 1

WHO Diagnostic Criteria for Cutaneous and Systemic Mastocytosis	
Cutaneous Mastocytosis (CM)	Typical clinical findings of urticaria pigmentosa(UP)/maculopapular cutaneous mastocytosis (MPCM) diffuse cutaneous mastocytosis (DCM) or solitary mastocytoma, and typical infiltrates of mast cells in a multi-focal or diffuse pattern on skin biopsy.
Systemic Mastocytosis (SM)	The diagnosis of SM is made if one major and one minor criterion are present, or, if three minor criteria are met.
Major Criterion	Multifocal, dense infiltrates of mast cells (15 or more in aggregates) detected in sections of bone marrow and/or another extracutaneous organ, and confirmed by tryptase immunohistochemistry or other special stains.
Minor Criteria	• In biopsy sections of bone marrow or other extracutaneous organs, more than 25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology, or, of all mast cells in bone marrow aspirates smears, more than 25% are immature or atypical mast cells. • Detection of an activating point mutation at codon 816 of KIT in bone marrow, blood or another extracutaneous organ. • Mast cells in bone marrow, blood or another extracutaneous organ express CD117 with CD2 and/or CD25. • Serum total tryptase persistently greater than 20 ng/ml in the absence of an associated clonal myeloid disorder.

TABLE 2

WHO systemic mastocytosis variants	
Cutaneous mastocytosis (CM)	Urticaria pigmentosa (UP)=maculopapular CM (MPCM) Diffuse CM (DCM) Mastocytoma of skin
Indolent systemic mastocytosis (ISM)	Smoldering SM Isolated bone marrow mastocytosis
Systemic mastocytosis with an associated clonal haematological non-mast-cell-lineage disease (SM-AHNMD)	SM-AML SM- MDS SM-MPD SM-CMML SM-NHL
Aggressive systemic mastocytosis (ASM)	
Mast cell leukaemia (MCL)	Aleukaemic MCL
Mast cell sarcoma	
Extracutaneous mastocytoma	

Abbreviations: SM, systemic mastocytosis; AML, acute myeloid leukaemia; MDS, myelodysplastic disease; MPD, myeloproliferative disease; CMML, chronic myelomonocytic leukaemia; NHL, non-Hodgkin lymphoma.

Figure 1 Typical lesions of urticaria pigmentosa (UP) appear on the chest and arms of an adult patient with ISM.

followed by diarrhea, nausea, and vomiting. Mild hepatomegaly is often seen in patients with long-standing SM, and may be accompanied by mildly elevated levels of liver enzymes. Aggressive forms of mastocytosis are associated with liver fibrosis, cirrhosis, ascites, and portal hypertension. Splenomegaly is observed in systemic disease. Bone pathology ranges from osteoporosis to osteosclerosis.

Cytopenias including anemia, thrombocytopenia, and neutropenia are common in aggressive forms of SM. Neutrophilia, monocytosis, and eosinophilia are also observed. Central and peripheral lymphadenopathy may occur.

MANAGEMENT

In adults, ISM tends to remain relatively stable or evolve slowly. Transformation from ISM into more aggressive forms of disease is unusual. Aggressive forms of disease, such as SM-AHNMD, often progress and may require interventional therapy directed at decreasing the mast cell burden and treating the associated hematologic disease.

Treatment of those with mastocytosis begins with symptom management with anti-mediator therapy. In most patients, symptoms are controlled using such drugs. If not controlled use of glucocorticoids may be considered. For those with skin disease, management includes good skin care, with preservation of moisture within the skin. Mastocytosis can be associated with spontaneous hypotension associated with an episode of mediator release (anaphylactic shock), which is managed in the same way as anaphylaxis in allergic patients without mastocytosis. Cytoreductive therapies including KIT-targeting tyrosine kinase inhibitors are reserved for the treatment of those with ASM, MCL, and SM-AHNMD. Referral to a center with expertise in managing rare forms of disease may be desirable.

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8 HYPERSENSITIVITY VASCULITIS

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KEY MESSAGES

- Patients with hypersensitivity vasculitis are usually adults, who develop palpable purpura and a maculopapular rash after an infection or the use of medication
- The biopsy of a skin lesion shows leukocytoclastic vasculitis and perivascular immune complexes that lack IgA
- Discontinuation of the eliciting drug or resolution of the underlying infection results in the resolution of skin signs and symptoms

INTRODUCTION, NOMENCLATURE AND CLASSIFICATION

Hypersensitivity vasculitis (HV) is one of the most common types of vasculitis seen by allergologists. Vasculitis is defined by blood vessel damage and the presence of inflammatory leukocytes in vessel walls. Vasculitides are categorized by the size of the blood vessels affected, i.e. small, medium and large vessel vasculitis. HV is a small vessel vasculitis.

CLINICAL PICTURE, DIAGNOSIS, AND TREATMENT

HV is typically caused by drugs (most commonly antibiotics such as penicillins, cephalosporins, sulfonamides, diuretics, NSAIDs, allopurinol, biologicals) or infections, viral (e.g. hepatitis B or C virus, parvovirus 19) or bacterial (e.g. streptococcal).

TABLE 1

American College of Rheumatology diagnostic criteria for hypersensitivity vasculitis
1. age >16 years,
2. use of a possible offending drug in temporal relation to the symptoms,
3. palpable purpura (figure 1),
4. maculopapular rash,
5. biopsy of a skin lesion showing neutrophils around an arteriole or venule.

HV signs and symptoms (palpable purpura and maculo-papular rash, figure 1) usually begin 7 to 10 days after the use of eliciting drugs or responsible infections. This period may be shorter with repeated antigen exposure. Acute HV usually resolves when the antigen is cleared, which is not always possible. Especially chronic hepatitis B or C virus infections can be associated with a more chronic course.

HV is diagnosed based on the typical clinical findings, the history (drug or infection) and a skin biopsy, showing leukocytoclastic vasculitis and perivascular immune complexes that lack IgA. Patients should be tested for serum complement levels, markers of inflammation (ESR/CRP), and cryoglobulins. HV is defined by the American College of Rheumatology criteria (Table 1). These criteria, however, do not reliably distinguish HV from IgA vasculitis (formerly called Henoch-Schönlein purpura). IgA vasculitis and HV are both immune complex-mediated, but IgA vasculitis shows internal organ involvement, whereas HV is, in almost all cases, limited to the skin.

The treatment of HV is the discontinuation of the provoking drug or antigen, which usually leads to the resolution of the signs and symptoms within a few days to weeks,

Figure 1 Palpable purpura and maculopapular rash in hypersensivity vasculitis.

but some cases remain idiopathic and become chronic. In severe or persistent cases antihistamines, colchicine, or dapsone may be helpful. Immunosuppressive drugs (e.g. glucocorticoids) should be reserved for patients with progressive disease, after infections have been ruled out as the underlying cause.

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Section F

SPECIAL CONSIDERATIONS

* Primary immunodeficiency diseases
* Allergic disease in the elderly
* Allergic diseases in pregnancy
* Allergic diseases and sports
* Allergic diseases in adolescents
* Adherence to the management plan
* Allergic diseases and quality of life
* Allergic diseases in animals

1 PRIMARY IMMUNODEFICIENCY DISEASES

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KEY MESSAGES

- The estimated prevalence of primary immune deficiency is underestimated
- Newborn screening for severe combined immunodeficiency (an immune deficiency that is uniformly fatal if not diagnosed and treated) has led to early diagnosis and treatment of these infants
- Hematopoietic stem cell transplantation has been a major advance in the cure for many primary immune deficiency disorders
- Immunoglobulin replacement therapy has led to improved outcomes in patients with antibody deficiency disorders
- More research is needed to reduce and identify comorbid conditions in patients with primary immune deficiency to improve outcomes and life expectancy

Primary immune deficiencies (PID) are a group of inherited disorders of the immune system that increase the susceptibility of the individual to severe and often difficult to treat infections, autoimmunity and in some patients malignancy. Over 200 genetic abnormalities that lead to a variety of PID have been identified. Approximately 250,000 people in the United States are diagnosed with PID, but according to estimates of the National Institutes of Health over 250,000 people are under diagnosed. In order to estimate the prevalence of PID in Europe as well as to establish and evaluate harmonized guidelines for the diagnosis and treatment of PID, the European Society for Immunodeficiencies (ESID) has developed an internet-based database for clinical and research data on patients with PID (Table 1).

About 55% of the PID are humoral or B-cell abnormalities, 25% are T-cell or combined T and B-cell immune deficiencies, 25% are phagocytic disorders, 25% are immune dysregulation syndromes, and <10% are complement deficiencies (Figure 1).

The most severe type of PID is lack of immune system at birth, e.g. absent T and B-cells (Severe combined immunodeficiency or SCID). SCID infants often die in the first year of life. Intervention with a bone marrow hematopoietic stem cell transplant is curative. Recent data shows that the prognosis of these infants is better if the diagnosis is made before 3 months of age for stem cell transplantation. Towards this goal in the United States newborn screening using quantification of T-cell receptor excision circles (TRECs) has been initiated in 15 states. This initiative has resulted in the early diagnosis and treatment of SCID infants, and has changed the incidence from 1:100,000 from older epidemiologic studies to a more recent estimate of <1:50,000 live births. Another approach to the treatment of SCID patients has been gene therapy.

27% of PID are diagnosed before age 6, but 51% are diagnosed after age 30. This latter group is mainly patients with B-cell immune deficiency, the most common of which is the Common Variable Immunodeficiency (CVID). The delay in diagnosis of these adult patients is 9-12 years and contributes to chronic lung disease and other comorbid conditions (Figure 2). Likewise, it is important to identify CVID patients early in order to start them on replacement im-

TABLE 1

Primary immunodeficiency prevalence based on reported cases in the European Society for Immunodefiencies (ESID) database*

Country	Alive PID patients documented	Population (millions inhabitants)	Documented PID patients per 100 000 inhabitants
France	2399	64 • 47	3 • 72
Ireland	76	4 • 24	1 • 79
Turkey	1083	70 • 59	1 • 53
United Kingdom	878	60 • 59	1 • 45
Estonia	15	1 • 34	1 • 12
Italy	655	59 • 13	1 • 11
Belgium	98	10 • 53	0 • 93
Poland	352	38 • 12	0 • 92
Czech Republic	88	10 • 31	0 • 85
Greece	89	11 • 17	0 • 8
Germany	552	82 • 24	0 • 67
Serbia	47	7 • 27	0 • 65
Switzerland	38	7 • 59	0 • 5
Slovakia	22	5 • 43	0 • 41
Sweden	32	9 • 18	0 • 35
Slovenia	6	2 • 02	0 • 3
Portugal	27	10 • 95	0 • 25

Total populations source: Wikipedia.
** Only countries with a prevalence >0.2 are displayed. Reproduced from Gathmann B, Grimbacher B, Beauté J, et al; The European internet-based patient and research database for primary immunodeficiencies results 2006-2008. Clin Exp Immunol. 2009;157(suppl 1):3-11 with permission from John Willey and Sons, Inc.*

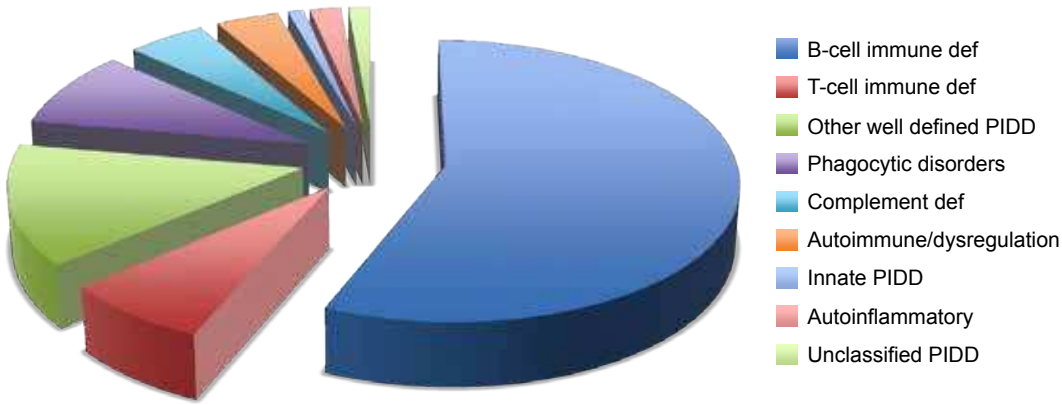

Figure 1 Distribution of Primary Immune Deficiency Diseases in the ESID registry database. (*Reproduced from Gathmann B, Grimbacher B, Beauté J, et al; The European internet-based patient and research database for primary immunodeficiencies results 2006-2008. Clin Exp Immunol. 2009;157(suppl 1):3-11 with permission from John Willey and Sons, Inc. Updated 2013 - 119 centers and 18,720 total patients. http://esid.org/Working-Parties/Registry/ESID-Database-Statistics accessed Jan 19, 2014.*)

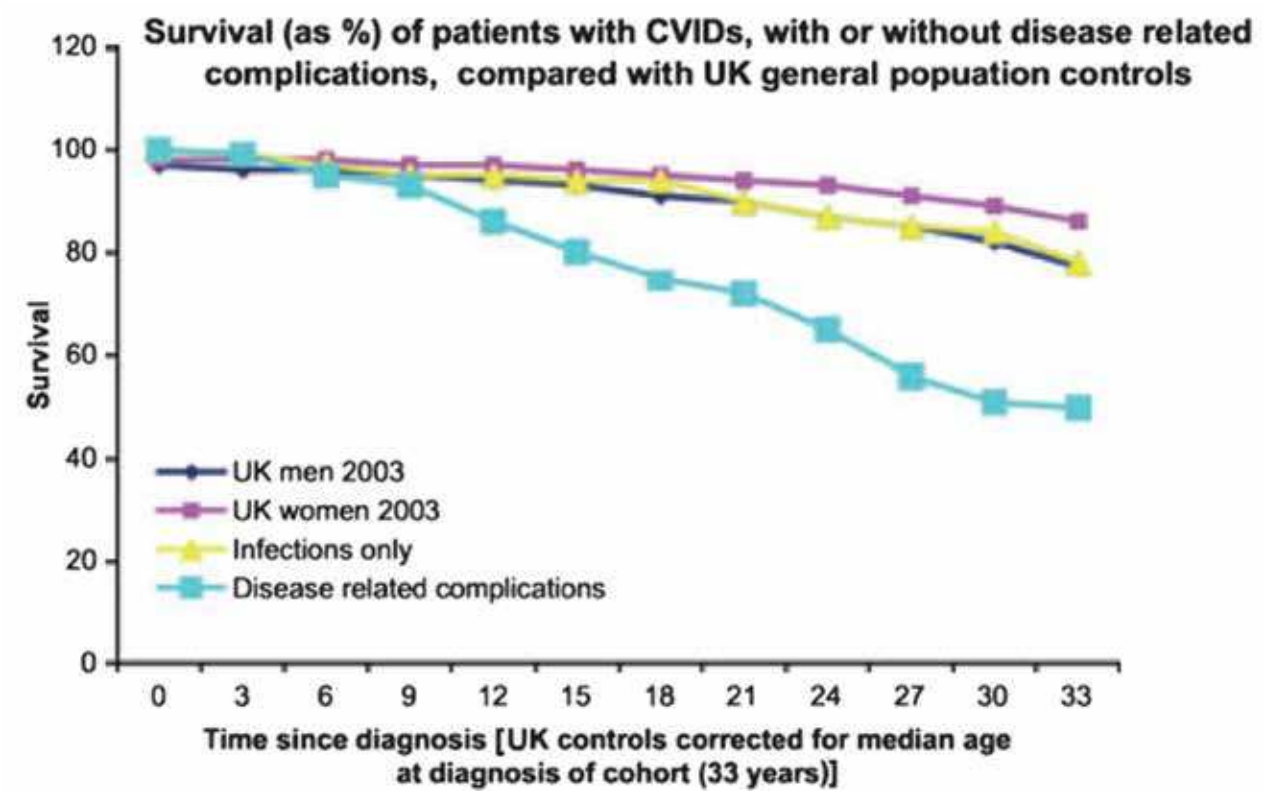

Figure 2 Survival of patients with CVIDs, by years since diagnosis and by clinical phenotype. Yellow line represents those patients without complications; Turquoise line represents those patients with at least one disease related complication. Kaplan–Meier plot of survival. (*Republished with permission of Blood, from Common variable immunodeficiency disorders: division into distinct clinical phenotypes, Chapel H, Lucas M, Lee M, et al,112,2,2008; permission conveyed through Copyright Clearance Center, Inc.*)

munoglobulin (Ig) therapy. Dosage requirements for optimal management of CVID patients have been recently discussed in several publications. The consensus by clinical immunologist is that the optimal dose of Ig therapy is the dose, which minimizes infection and improves patient outcome. Two routes for replacement Ig therapy are recommended either intravenous or subcutaneous. The latter has been utilized in Europe for several decades with advantages over the IV route of less systemic side effects, improved steady state serum IgG levels, home-based self-administration and better quality of life.

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2 ALLERGIC DISEASE IN THE ELDERLY

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KEY MESSAGES

- Asthma and allergic rhinitis are not uncommon in the elderly.
- Asthma in the elderly is heterogeneous in origin and often associated with loss of lung function
- Co-morbid conditions can affect treatment. Smoking adversely affects outcomes
- Additional research into pathophysiology and phenotypes is needed to improve treatment approaches

EPIDEMIOLOGY

The prevalence of allergic respiratory disease (allergic rhinitis and asthma) in the elderly is difficult to estimate due to differences in cut-off ages (≥55, ≥65, ≥75 e.g.). Nonetheless, in vitro assays for specific IgE in adults age ≥55 years in the U.S. showed that ~65% were sensitized to at least one allergen. However, a Swiss study found that only 26% of men and 18% of woman aged >60 years were sensitized. Skin prick testing of elderly Koreans found a similar lower rate of allergic sensitization (17-18%). Chronic rhinitis was also fairly common in the elderly Korean population (25%), but allergic sensitization did not show a significant association. The Swiss study found the prevalence of self-reported allergic rhinitis to be 13% for men and 15% for women ages >60 years. The lifetime prevalence of allergic rhinitis in adults (18-79) in Germany was similarly estimated to be 15%.

Of more concern is asthma in the elderly, which is difficult to estimate, because of confusion with COPD, the overlap of asthma with COPD, and confounding conditions like congestive heart failure. Reported incidence of newly diagnosed asthma in a U.S. population was 103/100,000 at age 65-74 years, 81/100,000 ages 75-84 years, and 58/100,000 age >85 years. Allergic sensitization does not appear to be a major factor in the development of asthma in the elderly.

The prevalence of asthma in the elderly is variable in different populations (Table 1), but appears to be rising over the past decade. Only 2% of Chinese citizens ages >50 self-reported having asthma. However, physician diagnosed asthma was higher in Hong Kong Chinese aged ≥70 years (4-5%). Doctor diagnosed asthma in Swiss citizens aged >60 years was 6.6% in men and 7.6% in women. Current asthma in U.S. citizens ≥65 years were similar at 6.3% (Table 1). Asthma death rate increases with age (Figure 1).

PROGNOSIS

Some 8-15% of older adults in the U.S. are annually admitted to the hospital. Often elderly adults lack a perception of dyspnea and hospitalized patients used peak-flow meters less often than younger patients and had less self-management knowledge. Women 50-60 years old being non-white and less educated appear to be at risk for hospitalization. Fortunately, when controlled for age, asthma is not associated with all-cause mortality. However, patients with asthma associated with COPD have worsened survival.

FUTURE RESEARCH

Asthma in the elderly presents diagnostic challenges defining the pathophysiologic mechanism, and further characterization of phenotype can lead to better treatments.

TABLE 1

Reported Prevalence of Asthma in Older Populations

Prevalence	Population	Age (years)
2%	Chinese, self-reported	>50
3.9%	Chinese, symptoms	>50
4-5%	Hong Kong, physician-diagnosed	≥70
6.6% males 7.6% females	Swiss, physician-diagnosed	>60
6.3%	U.S., NHANES study	≥65

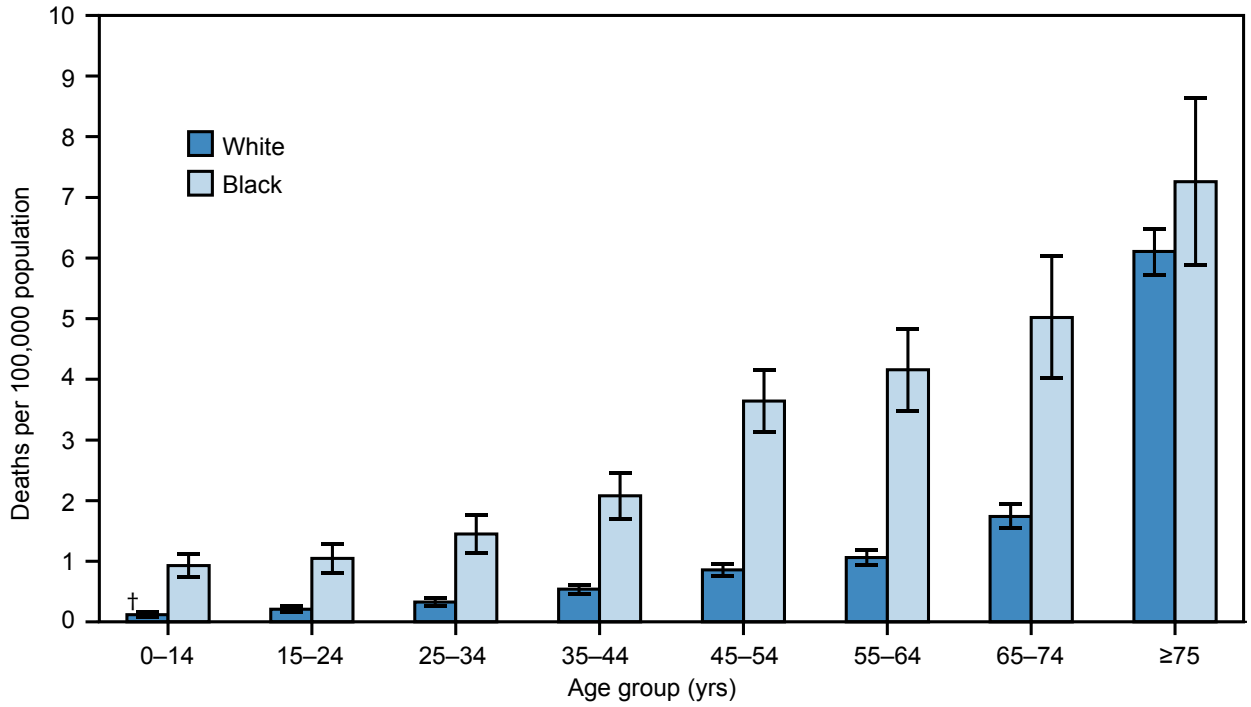

Figure 1 Asthma Death Rates by Race and Age, United States 2007-2009. *(From Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, 2012;61:315.)*

Smoking avoidance and cessation can clearly reduce the burden of asthma in the elderly.

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3 ALLERGIC DISEASES IN PREGNANCY

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KEY MESSAGES

- Pregnant asthmatics have a higher risk of adverse perinatal outcomes
- Unlike rhinitis of pregnancy, which presents with predominant nasal congestion symptoms, patients with allergic rhinitis often report prominent sneezing, nasal pruritus, and watery rhinorrhea, and some have concomitant ocular itching and irritation
- Treatment for urticaria during pregnancy may be necessary, if it is affecting quality of life
- Atopic dermatitis is the most common skin disorder observed during pregnancy
- Anaphylaxis is a rare event during pregnancy, but may be associated with severe maternal and neonatal complications

ASTHMA

A meta-analysis, derived from a substantial body of literature spanning several decades and including very large numbers of pregnant women, (over 1,000,000 for low birth weight and over 250,000 for preterm labor), indicates that pregnant women with asthma are at a significantly increased risk of a range of adverse maternal and fetal outcomes (Table 1). Suboptimal control of asthma or more severe asthma during pregnancy is associated with increased maternal or fetal risk.

Once the diagnosis of asthma is confirmed a decision regarding the need for controller medication versus rescue medication can be made (Table 2). Inhaled corticosteroids are the mainstay of controller therapy during pregnancy, but addition of long-acting beta agonists is appropriate, if required to achieve control. Adherence to therapy can change during pregnancy with a corresponding change in asthma control. Most commonly observed is decreased adherence as a result of a mother's concerns about the safety of medications for the fetus.

TABLE 1

Adverse fetal outcomes reported to be increased in infants of asthmatic women
Low birth weight
Preterm birth
Small for gestational age
Congenital anomalies
Stillbirth
Low APGAR scores at birth

ALLERGIC RHINITIS

Allergic rhinitis (AR) is usually preexisting, although it may develop or be recognized for the first time during pregnancy. Patients with AR often report prominent sneezing, nasal pruritus, and watery rhinorrhea, and some have concomitant ocular itching and irritation. Common triggers include dust mites, animal danders, molds, and pollens. The mainstays of therapy are avoidance of triggers, oral antihistamines and intranasal glucocorticoids. No important differences in efficacy or safety appear to exist between the various intranasal glucocorticoid preparations. Pregnant women who require antihistamines for AR should generally be treated with a second generation agent such as loratadine (10 mg once daily) or cetirizine (10 mg daily), since these drugs have reassur-

TABLE 2

Safety of commonly used medications for the treatment of asthma during pregnancy

Drug	FDA	Perinatal Outcome
Inhaled Bronchodilators		
Short-acting Bronchodilators	Albuterol(C)	Reassuring human data; some associations with specific malformations but may be chance or confounded by severity
Long-acting bronchodilators	Formoterol(C) Salmeterol(C)	Small amount of human data has been reassuring
Theophylline		No increase in congenital malformations; toxicity may be an issue
Systemic Corticosteroids		Associated with oral clefts, low birth weight, preterm birth, preeclampsia and intrauterine growth retardation. Some of these effects may be confounded by severity.
Inhaled Corticosteroids	Budesonide –B Beclomethasone-C Fluticasone_C Mometasone –C Triamcinolone -C	Substantial reassuring data. Risk of increased malformations with high dose, but may be confounded by severity. Most data for budesonide.
Leukotriene Receptor Antagonist	Montelukast –B Zafirlukast -B	Moderate amount of reassuring data
5-LO Inhibitor	Zileuton -C	Animal studies not reassuring; no human data
Anti-IgE	Xolair-B	Increased risk of low birth weight and preterm birth, but may be confounded by severity

Adapted from Schatz M, Zeiger RS, Falkoff R, Chambers C, Macy E, Mellon MH. Asthma and allergic diseases during pregnancy. In: Middleton' s Allergy: Principles and Practice, 8th ed, Adkinson, NF, Bochner BS, Burks AW et al (Eds), Mosby, St. Louis, MO 2014, pp. 951-69

ing animal and human data, are less sedating, and have fewer anticholinergic side effects compared with first generation (Table 3).

ATOPIC DERMATITIS

Atopic dermatitis (AD), or eczema is one of the most frequently observed skin diseases in pregnant patients. Most pregnant patients with AD present with lesions on the flexural aspects of the extremities, although truncal involvement is not uncommon. AD can change in severity during pregnancy, but has not been associated with an increased risk of perinatal complications such as congenital malformations. Similar to treatment of AR, the treatment for AD relies on avoidance of triggers and the judicial use of medications such as antihistamines for pruritus and topical corticosteroids (Table 4).

URTICARIA/ANGIOEDEMA

While there is no specific pregnancy-related urticaria, idiopathic urticaria may occur during pregnancy as well as urticaria due to any of the causes known to affect non-pregnant women.There have been no associations between presence of urticaria and adverse fetal outcomes. As in non-pregnant patients with urticaria, the treatment of choice is oral antihistamines, especially loratadine or cetirizine as noted above. Although not studied specifically in pregnancy for this purpose, leukotriene receptor antagonists such as montelukast (FDA Category B) may also be considered for recalcitrant urticaria, and may be continued, if started prior to pregnancy.

ANAPHYLAXIS

Anaphylaxis during pregnancy is considered a rare condition with an estimated prevalence of 2.7 cases/100,000 deliveries. Antibiotics are the most common trigger. If maternal oxygenation is compromised there may be associated fetal hypoxemia. Epinephrine remains the treatment of choice in pregnant patients. Anaphylactoid Syndrome of Pregnancy (ASP) is a rare complication of delivery in mother and/or infant during the process of birth. The maternal mortality rate worldwide for this complication is between 10 and 16%, while the fetal mortality rate is upwards of 30%. While the majority of infants will survive, the majority will also incur some form of neurologic defect. The pathophysiology is thought to be related to amniotic fluid or fetal cells entering maternal circulation. Mast cell degranulation appears to be a

TABLE 3

Safety of commonly used medications for the treatment of rhinitis during pregnancy

Drug Class	Drug/FDA Class	Adverse perinatal Outcome
Oral Antihistamines	Azelastine -C	No human data, animal studies show increase in teratogenicity, skeletal abnormalities and fetal death in high doses
	Cetirizine -B	No increase in congenital malformation
	Chlorpheniramine	No increase in congenital malformation
	Dexchlorpheniramine -B	No increase in congenital malformation
	Fexofenadine -C	This active metabolite of terfenedine has been associated with dose related weight gain animal studies.
	Diphenhydramine	No increase in congenital malformation ;withdrawal syndrome a risk
	Hydroxyzine	No increase in congenital malformations; withdrawal syndrome a risk
	Loratadine -B	No increase in congenital malformations, low birth weight, or small for gestational age
Decongestants	Oxymetazoline	No increase in congenital malformations; possible utero-placental insufficiency with higher doses
	Phenylephrine	Associated with club foot, eye/ear malformations
	Phenylpropanolamine	Increase in total and specific congenital malformations in one study, association with gastroschisis and VSD in case-control studies
	Pseudoephedrine	Association with gastroschisis, hemifacial microsmia and small intestinal atresia in some case-control studies
Intranasal Antihistamines	Azelastine	No controlled studies;
	Olapatadine	No controlled data; animal studies reassuring
Intranasal Corticosteroids	Budesonide –B Fluticasone -C Triamcinolone-C Mometasone-C	Substantial reassuring data for inhaled corticosteroids. Risk of increased malformations with high dose, but may be confounded by severity. Most data for budesonide.

Adapted from Schatz M, Zeiger RS, Falkoff R, Chambers C, Macy E, Mellon MH. Asthma and allergic diseases during pregnancy. In: Middleton' s Allergy: Principles and Practice,8 th. Adkinson, NF, Yunginger, JW, Busse, WW et al (Eds), Mosby, St. Louis, MO (in press)

TABLE 4

Treatment options for atopic dermatitis in pregnancy

Safe	Emollients, mild to moderate strength topical corticosteroids, oral antihistamines, ultraviolet B light
Relatively safe (caution)	Oral corticosteroids, cyclosporine, azathioprine, topical calcineurin inhibitors
Avoid	Methotrexate, mycophenolate mofetil, psoralens plus ultraviolet A light (PUVA)

prominent part of this syndrome. Symptoms typically include vascular collapse and disseminated intravascular coagulation. Treatment relies on controlling hemorrhage as well as vascular instability.

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4 ALLERGIC DISEASES AND SPORTS

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Physical exercise, although recommended for the general population and for allergic subjects, may represent a trigger of bronchial obstruction (in subjects with or without co-existing clinical asthma), rhino-conjunctivitis symptoms, skin manifestations and even severe anaphylaxis. Atopy has been shown to represent a risk factor for these conditions in both competitive and non-competitive exercisers.

KEY MESSAGES

- Physical activity is highly recommended to maintain health status and prevent chronic inflammatory conditions, including allergic diseases
- Exercise, however, may trigger bronchial, nasal, ocular, skin and even systemic symptoms, particularly in subjects with allergic diseases
- Accordingly, allergic diagnosis should be part of the routine medical examination in both competitive and non-competitive exercisers
- Early diagnosis of exercise-related symptoms and their adequate management may allow allergic subjects not only to practice sports safely, even at competitive level, but also to make physical exercise as a pillar of their therapeutic strategy
- Diagnosis and treatment of allergic diseases in elite athletes require special considerations in order to ensure the best performances, while respecting current anti-doping regulations

EXERCISE-INDUCED BRONCHOCONSTRICTION

Exercise-Induced Bronchoconstriction (EIB) represents a sign of poor asthma control. However, EIB may also occur in subjects with no evidence of clinical asthma, particularly in children, athletes, patients with atopy or rhinitis and following respiratory infections. The type, duration and intensity of physical exercise and environmental conditions are critical factors for the occurrence of EIB.

EIB recognizes a peculiar patho-physiological pathway. The hyperventilation, particularly of cold and dry air, causes water loss and increased osmolarity of the airways which results in epithelial damage and release of several inflammatory agents. Additional mechanisms have been suggested. Self-reported symptoms after exercise are not sufficient for a diagnosis of EIB, which has to be documented through pulmonary function tests before and after a standardized bronchial provocation. Exercise challenge or its surrogate indirect tests (Eucapnyc Voluntary Hyperpnea and Hypertonic Saline or Mannitol) are recommended. Direct bronchial provocation with histamine or methacholine is less accurate to document EIB, particularly in subjects without underlying asthma.

EIB is usually efficiently reversed by beta-2 adrenergic agent inhalation. The best preventive strategy for EIB in asthmatics is represented by achieving complete asthma control, according to GINA guidelines. Prevention of EIB in subjects without clinical asthma includes both pharmacologic and non-pharmacologic measures.

RHINITIS AND CONJUNCTIVITIS

Allergic rhino-conjunctivitis is a very frequent condition in exercisers. The type of sport influences mechanisms and symptoms (swimmer, winter, runner, boxer nose). Exposure to specific sensitizing allergens

Allergic rhinitis in 16/40 (40.0%)
NARES in 2/40 (5.0%)
Infective rhinitis 2/40 (5.0%)

"Swimmer's nose" in 20/40 (50.0%)

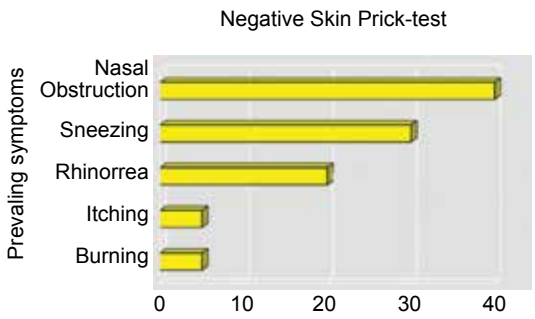

Figure 1 The swimmer nose: incidence, symptoms and inflammatory phenotype.

during in-door or out-door exercising may trigger or exacerbate nasal and ocular symptoms and affect performance. Rhinitis and conjunctivitis may also occur in non-allergic subjects: non-allergic rhinitis with neutrophilia has been reported in swimmers (Figure 1), possibly in relation to chlorine exposure, while cold air exposure may cause vasomotor rhinitis in winter athletes. Diagnosis and treatment do not differ from those recommended by ARIA guidelines in the general population. Particular attention should be placed on the potential negative effects on vigilance and reaction times of anti-histamines, particularly of those of the first-generation.

ALLERGIC SKIN DISEASES

Urticaria and angioedema may occur not only in relation to physical activity, but also to other factors connected to the specific sport practiced (pressure by sport instruments; exposure to water, cold, sun, etc.). Sports instruments and vests (often made by rubber) may cause allergic contact dermatitis and eczema in exposed sensitized individuals.

EXERCISE-INDUCED ANAPHYLAXIS

Exercise-Induced anaphylaxis (EIAn) is a rare, but unpredictable and severe, syndrome in which anaphylaxis occurs in conjunction with exercise. EIAn is often associated with food allergy and may only occur as a combination of exercise and ingestion of the sensitizing food (FDEIAn). Therefore, an accurate diagnosis of food allergy (including molecular diagnostics) has to be made in subjects with EIAn, and the sensiting food should be eliminated from the diet (possibly also avoiding any food ingestion in the three hours before exercising).

ALLERGIC DISEASES IN ELITE ATHLETES

Several studies indicate that sensitization and allergic diseases occur in elite athletes with a higher prevalence than in the general population (Figure 2). Suggested mechanism is the combined effect of a strenuous, chronic training and environmental exposure (allergens, pollutants, cold air, etc.) on both the immune system (with a switch to a Th2 cytokine profile, this also explaining the higher incidence of infections, particularly of the upper respiratory tract) and target organs. Diagnosis and treatment of allergic diseases in elite athletes require special considerations in order to ensure the best performances, while respecting current anti-doping regulations (Table 1).

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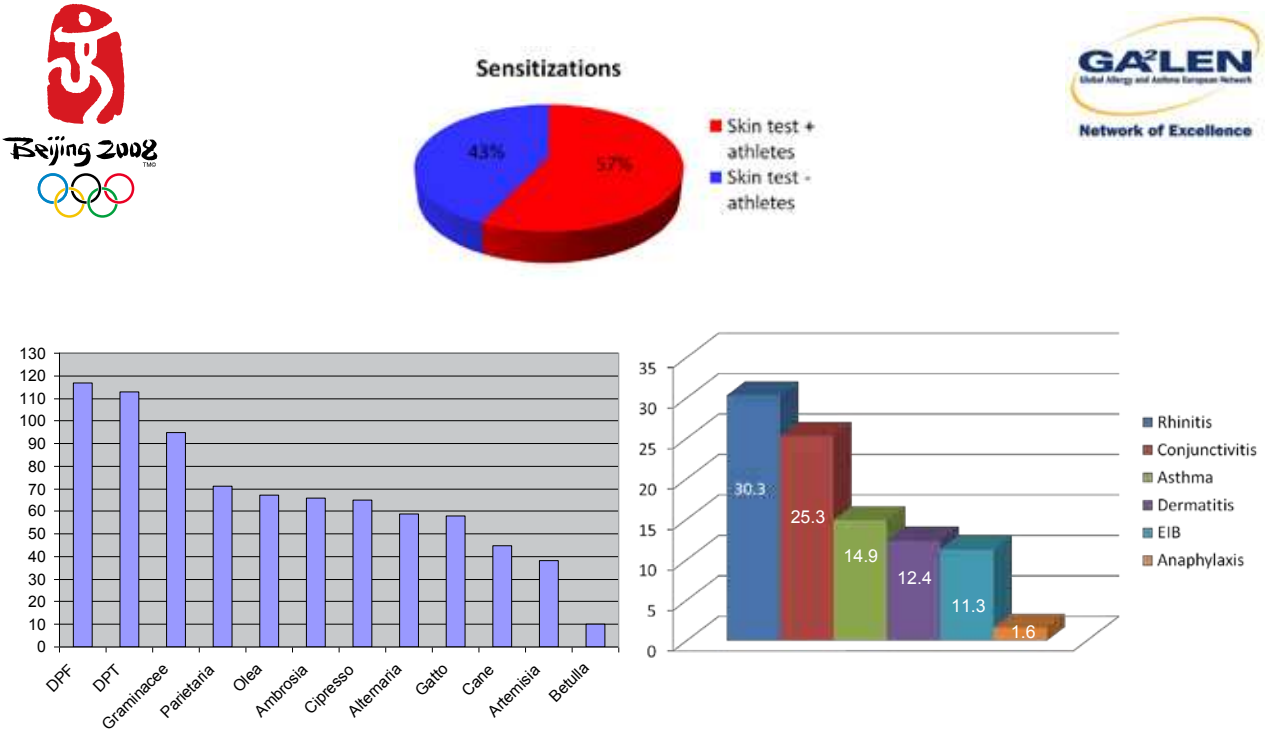

Figure 2 Prevalence of sensitization and allergic diseases in 378 Italian Olympic athletes (Bonini M. et al, 2014 submitted).

TABLE 1

WADA rules for anti-allergic drugs

Treatment	WADA Rules	Notes
Antihistamines	Permitted	Second generation molecules should be preferred to avoid side effects
Leukotriene modifiers	Permitted	
Inhaled steroids	Permitted	
Immunotherapy	Permitted	SCIT should not be performed before of after physical exercise
β2 agonists	Inhaled *Salbutamol (max 1600 mcg/24h)*	The presence in urine of salbutamol > 1000 ng/mL or formoterol > 40 ng/mL is presumed not be an intended therapeutic use of the substance and will be cnsidered as an Adverse Analytical Finding
	Formoterol (max 54 mcg/24H) and Salmeterol	
	All others prohibited in and out competition	
Systemic steroids	Prohibited in competition	
Ephedrine, methylephedrine	Prohibited in competition	A concentration in urine greater than 10 μg/mL represent an Adverse Analytical Finding

5 ALLERGIC DISEASES IN ADOLESCENTS

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KEY MESSAGES

- Many adolescents are affected by allergic diseases, and allergies have a major impact on their daily life
- The developmental milestones of adolescence can be challenging for patients, their parents and their clinicians
- Adolescent patients need to be approached in a way that promotes their development as active patients, who are empowered to take ownership of their allergies

IMPACT OF ALLERGY IN ADOLESCENCE

Many adolescents are affected by allergies. More than a third have symptoms of rhinoconjuctivitis, about 1 in 7 have asthma and around 1 in 50 have food allergy. This group experiences more morbidity and mortality than would be expected, they are overrepresented in fatal series of food allergy and asthma death registry data. Therefore adolescents deserve special attention in any allergy clinic.

ADOLESCENTS AS PATIENTS

Adolescence is a challenging time for any individual, even if they do not have a chronic medical condition. While coping with the physical changes associated with puberty, they have to start taking responsibility for themselves and others, gain independence, develop relationships outside their immediate families and renegotiate the rules at home (Figure 1).

All this may perhaps explain why adolescents are often poorly engaged with their healthcare provider. For example, despite follow up in an allergy clinic, adolescent patients often fail to avoid their triggering food allergens and carry their adrenaline autoinjector. There are similar issues with asthma. Looking at an allergy clinic from the adolescents' perspective, they may see consultations as being dominated by their parents, perhaps do not feel that clinic is relevant for them and may have issues around their confidentiality.

HOW CAN WE IMPROVE THE MANAGEMENT OF ADOLESCENT PATIENTS?

During adolescence, children must develop into independent adults with responsibilities for maintaining health status moving from parents to patient. Parents find this challenging, and adolescent may have limited opportunities to take on responsibility for their health. The management of adolescent patients, therefore needs to promote this transition.

There are a number of generic approaches that may help to engage adolescent patients:

- Ensure that adolescent patients are active participants in clinic using appropriate language, being empathic, respectful, and non-judgmental.
- Taking a patient rather than a

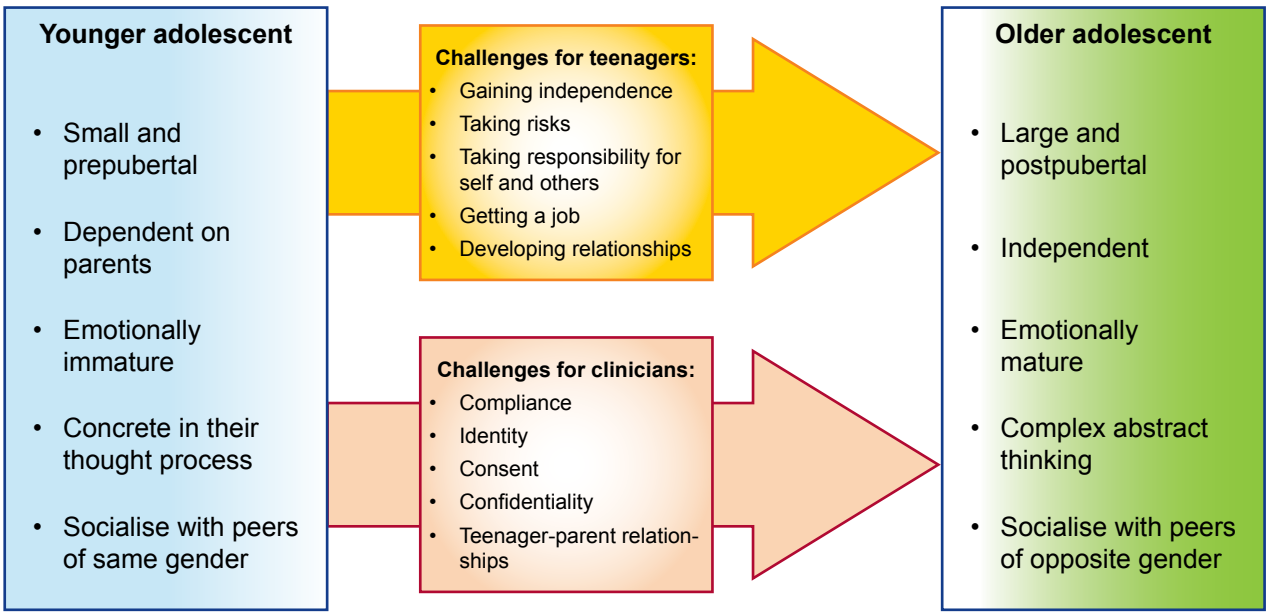

Figure 1 Adolescent development: challenges for patients and clinicians.

diseased centred approach may help adolescents realise the value of a clinic appointment.

- Slowly transition from parents. Seeing adolescent patients on their own for the initial part of the consultation may help to empower them to take ownership of their allergies.

For individual allergic diseases there are additional specific approaches that may be helpful. For asthma, for example, the focus should be on what activities asthma stops them doing and dealing with these by prescribing therapies that fit into their daily schedule. For food allergy, for example, education around the recognition and management of allergic reactions should be directed at the adolescent patient using scenario based role playing and adrenaline autoinjector simulators.

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6 ADHERENCE TO THE MANAGEMENT PLAN

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KEY MESSAGES

- Adherence is the extent to which a patient's behavior reflects the "agreed upon" the management plan as outlined by their healthcare provider
- Barriers to adherence are numerous and include disease and patient specific concerns, as well as, provider practice pattern, health system constraints, and the larger societal context
- Strategies to improve adherence include written action plans, simplification of treatment regimens, and novel technologies such as social media or text messaging (SMS)
- Shared decision making between patients and provider is crucial in constructing an effective treatment plan and improving adherence

The global burden of non-adherence in allergic diseases is substantial. Developing an optimal management plan in allergic diseases depends equally on appropriate medication recommendations as well as the patient's ability and desire to adhere to the proposed treatment. Adherence is the extent to which a patient's behavior resembles the "agreed upon" management plan as outlined by their healthcare provider. The qualification of 'agreed upon' emphasizes the importance of shared decision making between patient and their providers. Adherence contrasts the term compliance, which conceptualizes the patient's role as limited to following recommendations, without explicit consideration of patient's preferences and goals. In allergic disease, adherence issues have been most fully explored in asthma care, primarily due to the increased availability of traceable outcome measures, such as exacerbation rates, systemic corticosteroids use, emergency department visits, and hospitalizations.

Patient's adherence to the "agreed upon" management plan can be difficult to assess and sometimes not evident until poor outcomes are suffered. Barriers to adherence are numerous and include chronicity of disease, increasingly complex medication regimens, high medication cost, and lack of perceived treatment benefit (Figure 1). Assessing the level of adherence is crucial and can be accomplished by direct patient interviewing, pharmacy fill rate, medication monitoring methods (pill counting, inhaler dose counters, etc) or through biochemical assays. Exhaled nitric oxide is emerging as a potentially powerful bioassay for measuring inhaled corticosteroid adherence in patients with asthma.

Improve adherence is critically important in the management of allergic diseases. Written Action Plans (WAPs) may be a useful tool for the practicing allergist to enhance patient understanding of the management plan (Figure 2). In the acute care setting, WAP have been shown to significantly increase patient adherence to inhaled corticosteroids, improve asthma control, and medical follow up. WAPs are available for a number of allergic diseases including anaphylaxis and allergic rhinitis. Simplifying the management plan can also improve patient adherence (Figure 3).

The widespread availability and acceptability of technologic inter-

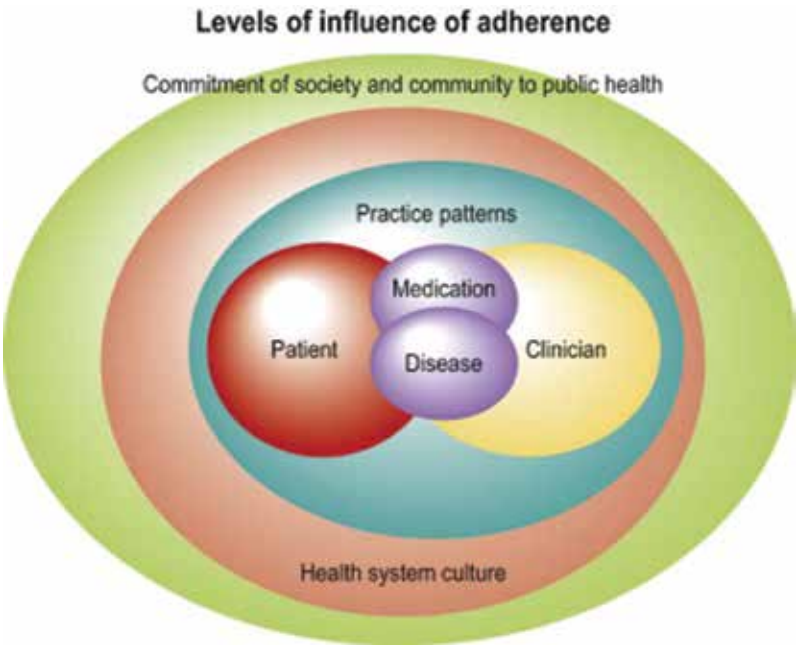

Figure 1 Barriers to adherence are numerous and are influenced by a multitude of levels. Societal concerns and the health system culture set the stage for the patient-provider interaction. On an individual level, a clinician's practice pattern and the patient's individual preferences and goals affect the milieu in which the treatment plan is made. The particulars of the disease and the available medications make up the specific variable of this complex equation. (*Reproduced from Middleton's Allergy: Principles and Practice, 8ed, Apter A, Bender B, Rand C, Ed. Adkinson et al, Adherence, 1473, copyright 2013 with permission from Elsevier.*)

Figure 3 This patient found herself overwhelmed by a complex treatment plan for her allergic diseases. Simplification of treatment regimens, as well as, understanding patient's treatment preferences and goals lead to improved adherence.

ventions, such as text messaging or social media, may be useful tool in improving adherence rates and evidence on this topic is emerging.

Of all the potential interventions aimed at improving patient adherence, striving to strengthen the provider-patient relationship and focusing on management plans that takes the patient's preference into account may lead to optimal treatment outcomes in allergic diseases.

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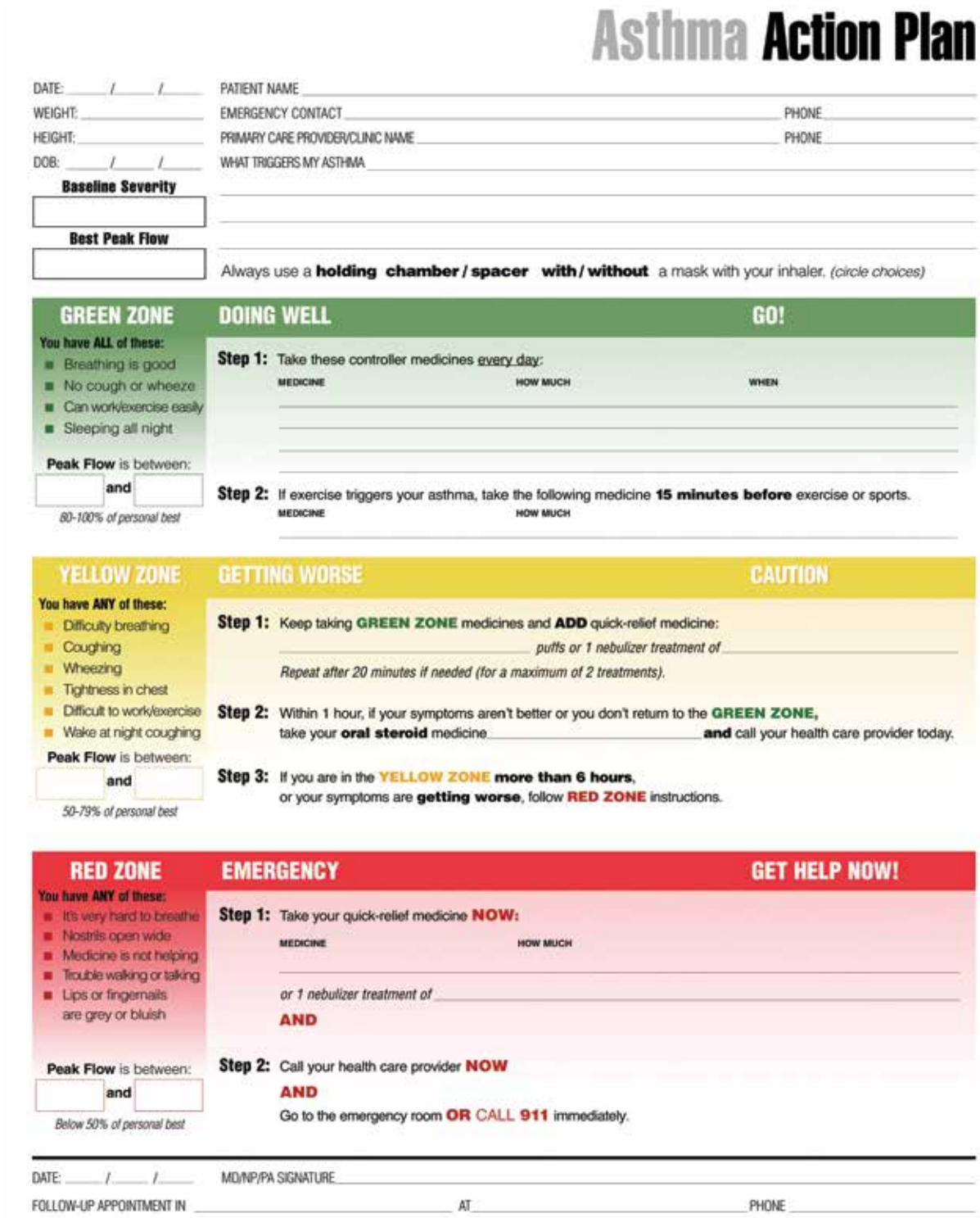

Asthma Action Plan

DATE: ____/____/____ PATIENT NAME ____

WEIGHT: ____ EMERGENCY CONTACT ____ PHONE ____

HEIGHT: ____ PRIMARY CARE PROVIDER/CLINIC NAME ____ PHONE ____

DOB: ____/____/____ WHAT TRIGGERS MY ASTHMA ____

Baseline Severity

Best Peak Flow

Always use a **holding chamber / spacer with / without** a mask with your inhaler. *(circle choices)*

GREEN ZONE — DOING WELL — GO!

You have ALL of these:
- Breathing is good
- No cough or wheeze
- Can work/exercise easily
- Sleeping all night

Peak Flow is between: ____ and ____
80-100% of personal best

Step 1: Take these controller medicines every day:

MEDICINE	HOW MUCH	WHEN

Step 2: If exercise triggers your asthma, take the following medicine **15 minutes before** exercise or sports.

MEDICINE	HOW MUCH

YELLOW ZONE — GETTING WORSE — CAUTION

You have ANY of these:
- Difficulty breathing
- Coughing
- Wheezing
- Tightness in chest
- Difficult to work/exercise
- Wake at night coughing

Peak Flow is between: ____ and ____
50-79% of personal best

Step 1: Keep taking **GREEN ZONE** medicines and **ADD** quick-relief medicine:
____ *puffs or 1 nebulizer treatment of* ____
Repeat after 20 minutes if needed (for a maximum of 2 treatments).

Step 2: Within 1 hour, if your symptoms aren't better or you don't return to the **GREEN ZONE,** take your **oral steroid** medicine ____ **and** call your health care provider today.

Step 3: If you are in the **YELLOW ZONE** **more than 6 hours,** or your symptoms are **getting worse**, follow **RED ZONE** instructions.

RED ZONE — EMERGENCY — GET HELP NOW!

You have ANY of these:
- It's very hard to breathe
- Nostrils open wide
- Medicine is not helping
- Trouble walking or talking
- Lips or fingernails are grey or bluish

Peak Flow is between: ____ and ____
Below 50% of personal best

Step 1: Take your quick-relief medicine **NOW:**

MEDICINE	HOW MUCH

or 1 nebulizer treatment of ____

AND

Step 2: Call your health care provider **NOW**

AND

Go to the emergency room **OR** CALL **911** immediately.

DATE: ____/____/____ MD/NP/PA SIGNATURE ____

FOLLOW-UP APPOINTMENT IN ____ AT ____ PHONE ____

Figure 2 Written Action Plans, such as this Asthma Action Plan, may be a useful tool for the practicing allergist to enhance patient understanding of the management plan. Written Action Plans are available for a variety of allergic disease including anaphylaxis, food allergy, asthma, and eczema. Reproduced from the Minnesota (USA) Department of Health with permission. Accessed January 27, 2014. URL: http://www.health.state.mn.us/divs/hpcd/cdee/asthma/ActionPlan.html

7 ALLERGIC DISEASES AND QUALITY OF LIFE

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Allergic diseases are rarely fatal. Even the most extreme and severe form of allergy, anaphylaxis, has a low mortality rate. Allergic diseases rarely lead to traditional forms of infirmity, and societal awareness and concern regarding allergic diseases has thus been limited. However, research carried out over the last decades has shown that allergic diseases significantly impact quality of life (QoL) of patients, and this knowledge has dispelled many notions of allergy as being a "trivial" disease. Despite this, misunderstandings about the correct development and use of instruments measuring QoL may give the impression that these outcomes are "soft" and subjective. In fact, proper application of good instruments generates outcomes that are neither.

KEY MESSAGES

- Health-related quality of life (HRQL) is one of the most important outcomes in studies on allergic diseases
- HRQL may be accurately measured using instruments developed for this purpose
- HRQL is unjustifiably underutilized in clinical studies
- Use of HRQL in clinical practice requires further research

HEALTH-RELATED QUALITY OF LIFE: WHAT MATTERS TO PATIENTS?

Health-related quality of life (HRQL) is that part of overall QoL, which is affected by health and disease (Figure 1). The most important aspect of questionnaires measuring HRQL is that they are properly validated, as it is this process, which ensures that non-disease-related QoL issues are excluded and that only HRQL is measured. Many instruments have also ascertained the minimal clinically important difference (MCID), which represents the smallest change or difference in HRQL scores, which is clinically meaningful to patients. Thus, HRQL instruments can accurately measure aspects of disease important to patients. In addition, they can show if changes, for example brought about by treatment are relevant from the patient's point of view.

MEASURING HEALTH-RELATED QUALITY OF LIFE IN ALLERGIC DISEASES

Over the past 25 years, instruments for measurement of HRQL have been developed for rhinitis, asthma and atopic dermatitis, allergic diseases which tend to be

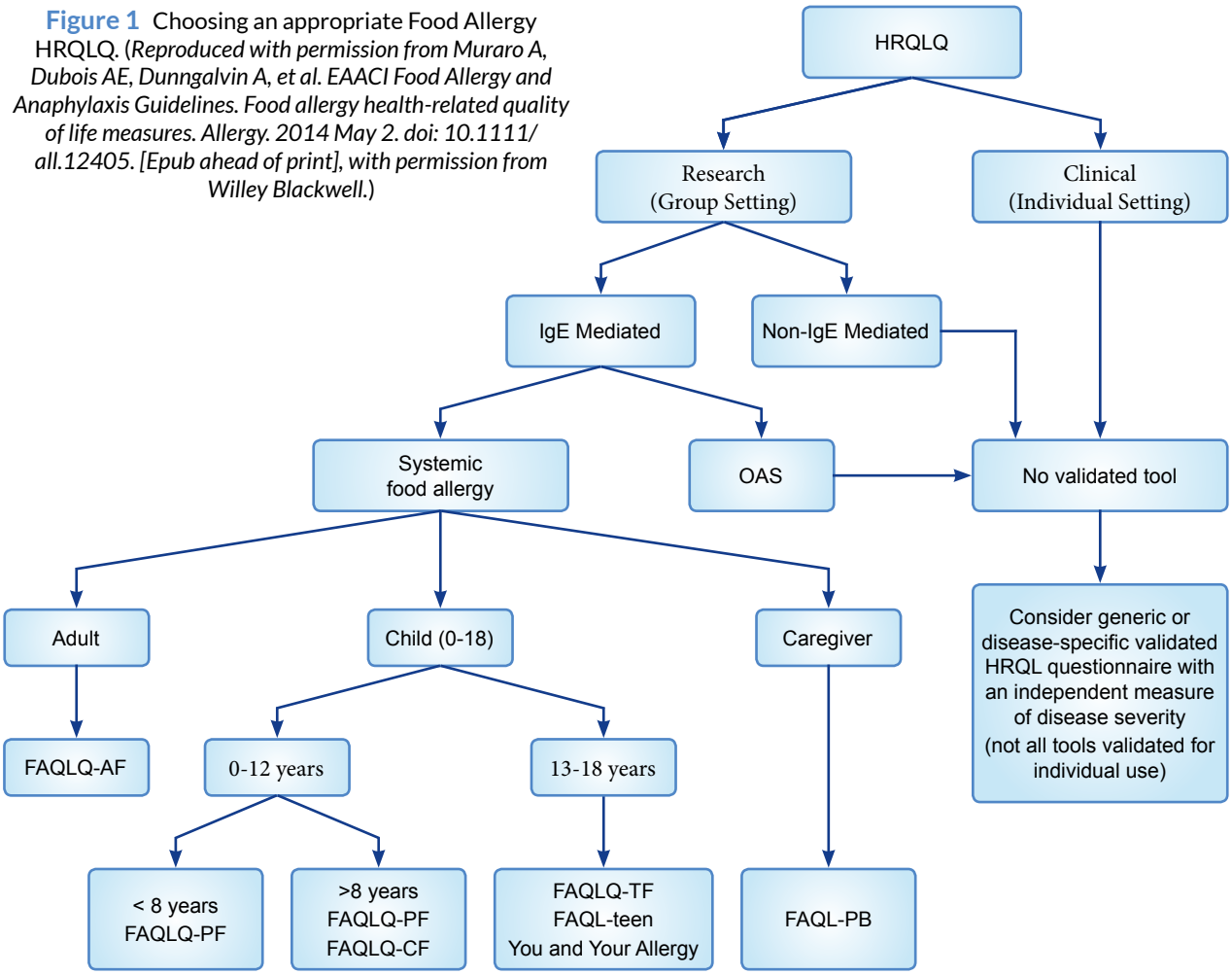

Figure 1 Choosing an appropriate Food Allergy HRQLQ. (*Reproduced with permission from Muraro A, Dubois AE, Dunngalvin A, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Food allergy health-related quality of life measures. Allergy. 2014 May 2. doi: 10.1111/all.12405. [Epub ahead of print], with permission from Willey Blackwell.*)

chronic and where the impact on HRQL is of paramount importance in the assessment of management. More recently, instruments have been developed for measuring HRQL in patients at risk for anaphylaxis, both from vespula venoms and foods, where the expectation of outcome of future episodes and consequent avoidance behavior, rather than chronic symptoms, drives HRQL. The choice of the correct tool to measure HRQL is essential (Figure 2).

Despite the eminent suitability of these measurements for research purposes, HRQL is usually a secondary rather than a primary outcome in most studies. Ironically, symptom-medication scores, which are frequently used instead, are difficult to interpret, because it is usually unknown what changes are big enough to be important to patients. Application of HRQL measures in clinical practice is limited by the lack of studies formally assessing the contribution of this information to management.

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8 ALLERGIC DISEASES IN ANIMALS

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Hypersensitivity disorders represent a major burden for companion and large animals, especially dogs, cats and horses. The other species are probably also affected even though data are only sparse. Major allergens include insect (flea, flies), environmental (house dust and storage mites, pollens, molds, epithelia) and food allergens. From a clinical point of view, the skin and the gastrointestinal tract are by far the most frequently affected, even though horses and cats may present with clinical signs of allergic asthma.

KEY MESSAGES

- Hypersensitivity disorders, particularly allergy is frequent in animals and affect all commonly treated species
- The main target organs are the skin and the intestinal tract even though a counterpart of asthma is recognized in cats and horses
- Atopic dermatitis, the most frequent allergy in dogs and cats, affect up to 50% of individuals in some predisposed breeds
- Treatment of allergic disorders in animals is mainly based on allergen avoidance, use of immunomodulatory drugs and allergen-specific immunotherapy

Insect allergies were the first well characterized allergy disorders in animals and are considered to be type I and type IV hypersensitivity reactions. In dogs and cats, fleas are frequently involved and flea hypersensitivity dermatitis was long considered the first cause of skin disorders in both dogs and cats. In horses numerous flies have been suspected to induce similar disorders. Affected animals present with intense itch usually localized on the dorsal aspect of the body. In contrast, bee and wasp allergies are comparatively rare in domestic animals and are usually associated with urticaria, angioedema and/or anaphylaxis.

Environmental allergies mostly target the skin in animals. Atopic dermatitis is the most frequent diseases in dogs and in some breeds (French Bulldog, Shar pei, West-Highland-White Terrier more than 50% of individuals are affected. Affected animals present with itch and erythema usually localized to the head, feet and ventral parts of the body (Figure 1). Canine atopic dermatitis is considered the counterpart of human disease and most of the findings observed in humans are applicable to the dog. In fact, canine atopic dermatitis is a Th2 driven disorder in the acute phase of the disease and is mainly Th1 in the more chronic one. The most frequently involved allergens are house dust mites even though similar symptoms have been observed with pollen and food allergies. AD is less well characterized in cats, horses and other domestic animals but the disease is recognized in all of these species.

Mites and pollen allergens are also involved in the pathogenesis of equine and feline asthma. Equine heaves is a spontaneous occurring asthma-like condition affecting 10–20% of adult horses in the northern hemisphere and other temperate climates. Similarly to asthma, heaves is a chronic disorder of the airways, which is characterized by variable and recurring airflow obstruction, bronchial hyperresponsiveness and airway inflammation. During disease exacerbation, horses present increased respiratory efforts at rest, coughing and exercise intol-

Figure 1 Atopic dermatitis in a dog.

erance. Clinical signs are triggered or exacerbated by inhalation of dust particles present in the stables, especially those associated with hay feeding. Neutrophils and macrophages are present in large numbers in the airways of horses with heaves and may contribute to the disease through the release of several inflammatory mediators. Experimental models of feline asthma have been developed with cats sensitized to various allergens including mites and pollens. Similarities of horse heaves with the human asthma are currently being used to evaluate airway remodelling and its reversibility in ways that are not possible in humans for ethical reasons. Research perspectives that can be relevant to asthma include the role of neutrophils in airway inflammation and their response to corticosteroids, systemic response to pulmonary inflammation, and maintaining athletic capacities with early intervention.

Treatment of allergic disorders in animals is mainly based on allergen avoidance (insects: use of antiparasitic treatment avoidance or organic dust for heaves), use of allergen-specific immunomodulatory (AIT) drugs such as glucocorticoids or cyclosporine and desensitization. AIT is mainly used for the treatment of atopic dermatitis in dogs and cats and is successful in about 60-70% of the cases. Bronchodilators and corticosteroids are administered systemically or by inhalation in heaves to provide rapid relief of airway obstruction, or when control of the environment is partial or absent.

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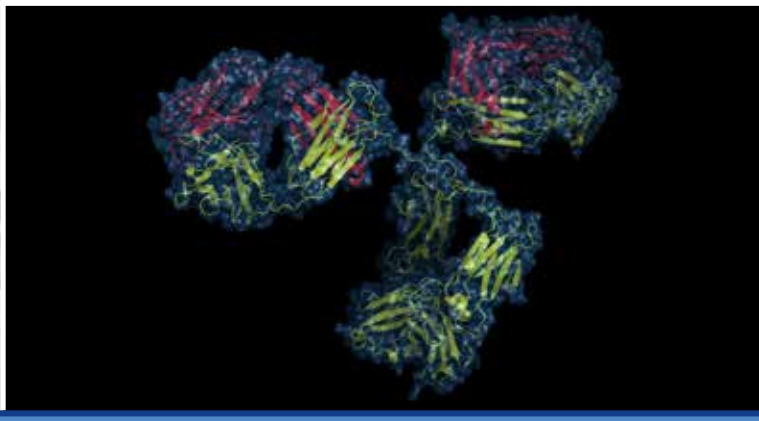
Section G



MANAGEMENT OF ALLERGIC DISEASES

* Overview: avoidance, treatment, induction of tolerance
* Avoidance measures in the management of allergic diseases – focus on environment
* Avoidance measures - focus on diet
* Perinatal risk factors and strategies for allergy prevention
* Pharmacological treatment of allergic disease
* Anti IgE treatment for allergic disease
* Biological agents for the treatment of allergic disorders
* Biosimilars and allergy treatment
* Targeting basophils and mast cells for novel treatment approaches
* Tolerance induction: principle and modalities
* Allergen immunotherapy- overview
* Mechanisms of allergen immunotherapy
* Subcutaneous allergen immunotherapy
* Sublingual allergen immunotherapy
* Oral allergen Immunotherapy for foods
* Recombinant allergens for allergen immunotherapy
* Peptide immunotherapy for allergic disease
* New routes for allergen immunotherapy
* Measuring clinical outcomes in allergen immunotherapy
* Implementing a healthy life style
* Psychological support in the management of allergic patients
* Pharmacogenetics and pharmacogenomics of allergic diseases
* Pharmacoeconomics of allergic diseases

1 OVERVIEW: AVOIDANCE, TREATMENT, INDUCTION OF TOLERANCE

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KEY MESSAGES

- The management of allergic diseases will depend on three main factors: (a) how easy it is to avoid the trigger, (b) whether there are multiple triggers and (c) how easy it is to induce tolerance
- Drug treatment for allergies focuses on blockade of key mediators of inflammation and more broadly on anti-inflammatory agents, which block the activation of key cytokines which augment and sustain airways inflammation
- More targeted therapies are useful in selected patients
- Allergen-specific immunotherapy induces tolerance by deviating the immune response away from the allergic pattern

Allergy is a trigger for a variety of conditions. Allergy testing is directed towards establishing which triggers, if any, are responsible for the particular problems a patient experiences. Once an allergic trigger has been identified, the management plan will depend on three main factors: (a) how easy it is to avoid the trigger, (b) whether there are multiple triggers and (c) how easy it is to induce tolerance (Figure 1).

The possibility of avoidance depends on the source for airborne allergens. Pollens and mould spores may be ubiquitous and so avoidance measures are impossible. In contrast, occupational allergens may be contained by alterations to manufacturing processes or air supply system. Animal danders may be avoidable in ones own home, but may be a problem, if the patient has to visit other homes in the course of their work. Exposure to house dust mite allergens can be contained by exclusion covers, but has not always proved as effective as one might hope. In part, this may reflect the existence of multiple triggers, but it is also possible that the mechanisms, which lead to the induction of perennial allergic asthma and rhinitis are not the same as those which lead to its perpetuation. Extreme forms of dust mite avoidance, through living at high altitude, appear more effective than the measures that can be achieved as sea level (Table 1).

Drug treatment for allergies focuses on blockade of key mediators of inflammation (e.g. antihistamines and anti-leukotrienes) and more broadly on anti-inflammatory agents, principally glucocorticoroids, which block the activation of key cytokines which augment and sustain airways inflammation. For full-blown anaphylaxis, self-administered adrenaline injection can be life-saving. More targeted therapies include monoclonal antibodies against IgE and against various pro-allergic cytokines (e.g. anti-IL-5). Although expensive, these therapies are useful in the management of selected patients.

Tolerance implies that the individual either ceases to react or has a reduced reaction on exposure to allergens, which previously caused symptoms. Specific immunotherapy can do this by deviating the immune response away from the allergic pattern. The results are more impressive for anaphylaxis to insect venom than for airborne allergies, but there is no doubt some patients do extremely well. Recent reports of inducing tolerance in peanut allergy suggest that there is scope for further development of tolerance induction as a means of controlling food-related anaphylaxis.

TABLE 1

Studies investigating allergen avoidance in infancy

	CCAPPS	PREVASC	SPACE
Country	Canada	Netherlands	Europe
Study population	High Risk	High Risk	High Risk
Design	Prospective randomised controlled trial to determine the effectiveness of a multifaceted intervention programme in the primary prevention of asthma in high risk infants in two Canadian centres.	A multi-faceted intervention study to reduce environmental exposure to inhalant and food allergens and cigarette smoke in genetically susceptible children.	A prospective randomised controlled trial of multifaceted design.
Intervention	Allergen impermeable covers Weekly bed sheet laundering Acaricide washes Removal of pets Smoking cessation advice Breast feeding encouraged for entire first year Delay introduction of solids until 6 months Cow's milk, peanuts and seafood discouraged in infancy. Avoid day care until after the first year	Pets to be kept outside. Allergen impermeable covers Exclusive breast feeding to 6months Smoking cessation advice Avoid solid food and cow's milk until 6 months.	Exclusive breast feeding for as long as possible Delay solids until 6 months. Cow's milk, egg and fish avoided until 12 months. Peanut/tree nut avoided until 3 years. Allergen impermeable bed covers Remove carpet from the infant's room Hot wash soft furnishings weekly Ventilate infant's room at least once a day and vacuum weekly Pets and smoking discouraged.
Numbers	545	476	696
Age last assessed	7 years	6 years	2 years
Clinical outcome	The proportion of children with probable asthma (as defined by wheeze in the last 12 months plus bronchial hyper-responsiveness) was lower in the intervention group when adjusted values were used 25% vs. 12.9% (p= 0.002)(39). Bronchial hyper-responsiveness was not statistically different between the two groups.	No significant influence on the diagnosis of asthma diagnosis at the age of 6 years. There was also no effect on the lung function tests.	No significant difference between the two groups in the diagnosis of asthma/ wheezy bronchitis (18.1%in the active vs. 17.8% in the control group) (54). The number of children sensitised to HDM allergen was lower in the active group, but this was probably not significant (1.86% vs. 5%).
Additional information	More of the intervention group had been to hospital emergency departments with wheeze in the preceding 12 months. The level of house dust mite allergen found in the homes of each group was significantly different however there was no significant difference in the SPTs between the two groups.	HDM exposure is low in the Netherlands making improvements difficult. The number of weeks children were breast fed didn't significantly differ between the groups.	It was postulated that HDM induced asthma usually presents later in childhood and an effect may be seen at a later date, however a follow up was published at 24months which did not show any evidence of an improvement in symptomatic allergy and no further follow up studies have been published.

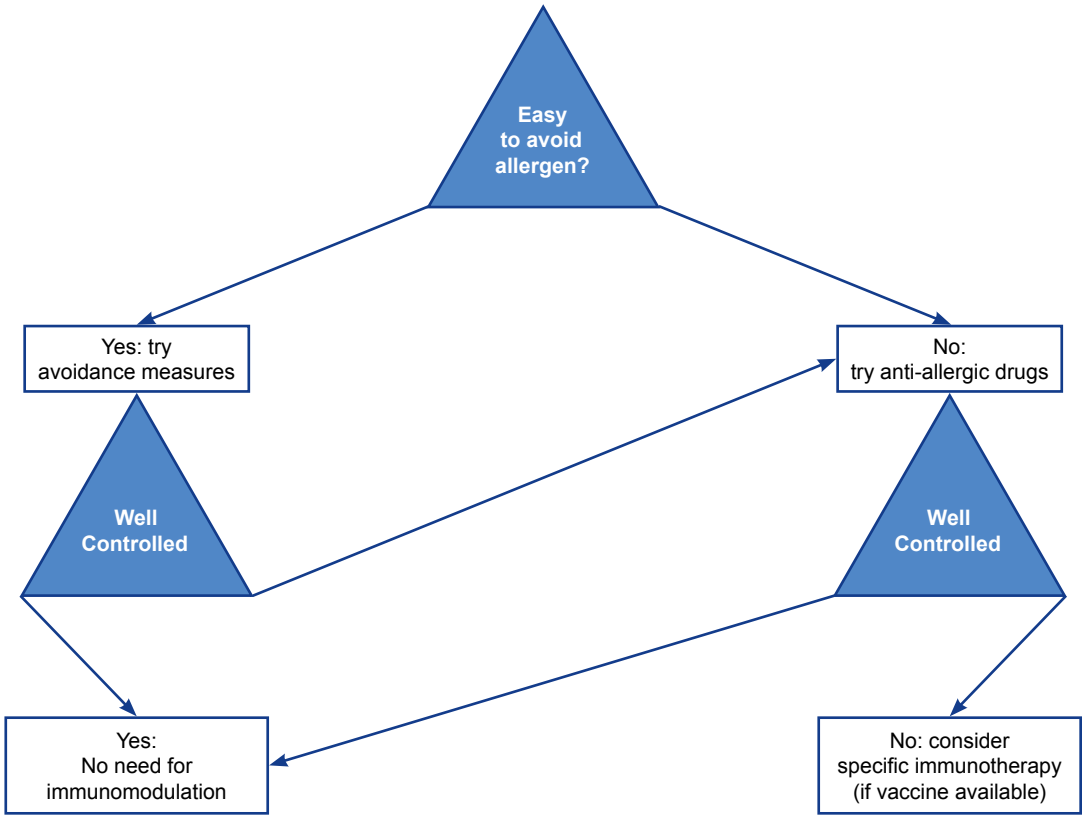

Figure 1 Step-wise management of allergic diseases.

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2a AVOIDANCE MEASURES IN THE MANAGEMENT OF ALLERGIC DISEASES – FOCUS ON ENVIRONMENT

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KEY MESSAGES

- Several allergic manifestations of the upper and lower airways as well as the skin may exacerbate upon environmental exposure to outdoor or indoor allergens
- Causal relationship between environmental allergens and allergic symptoms is suggested by targeted avoidance and reexposure
- Exposure related allergies can be reproduced artificially in the lab or exposure chambers
- Complete avoidance of outdoor allergens in most cases is unrealistic. Avoidance of indoor allergens should always be tried as a first treatment of choice, however, results are variable and complete avoidance is not easy to achieve

Sensitization to environmental allergens may occur throughout life, however, the first two decades of life show the highest incidence of IgE-antibody-development to outdoor (pollen and moulds) or indoor (dust mite, cockroaches, pets, moulds) allergens.

Sensitization usually precedes the manifestation of clinical symptoms by months or years. It has be shown to be determined by genetic susceptibility, following a dose dependent risk. Children growing up in a domestic environment with high levels of indoor allergens from pets or mites who develop sensitization during the first years of life, have been shown to have a significantly increased risk for lung function impairment during school age and for chronic persistence of allergic asthma. Therefore allergen avoidance or at least reduction of allergen exposure to the lowest possible level has always been a key element of the allergic patient care.

OUTDOOR ALLERGENS

Given the fact that pollen with the greatest allergological relevance may be carried by wind for long distances, it is obvious, that complete outdoor allergen avoidance is not realistic in most cases. Textbooks are usually recommending to stay indoors, close the windows or wash the hair, once it is contaminated by allergenic pollen, however, these recommendations are rather pragmatic and not really based on scientific evidence. Another pragmatic approach is to travel to privileged sites with low aeroallergen exposure during the main pollen season (seaside, high altitude resorts).

INDOOR ALLERGENS

The key indoor allergens with global relevance are produced by different species of house dust mite (HDM). Growth and reproduction of mites is facilitated by modern house insulation, higher temperatures and particularly high indoor humidity. Wall to wall carpets may also contribute to higher HDM allergen level. Human exposure is particularly high during the night, since dust mites are found in mattresses at the highest concentrations (figure 1). While frequent vacuum cleaning and acaricides have been shown to be of insufficient, specific mattress encasing (Figure 2) which allows the exchange of humidity but not the transfer of allergens have been demonstrated to be useful barriers between the human body and dust mites in the mattress (Figure 3). In monosensitised asthmatic children these encasings are not only able to reduce aller-

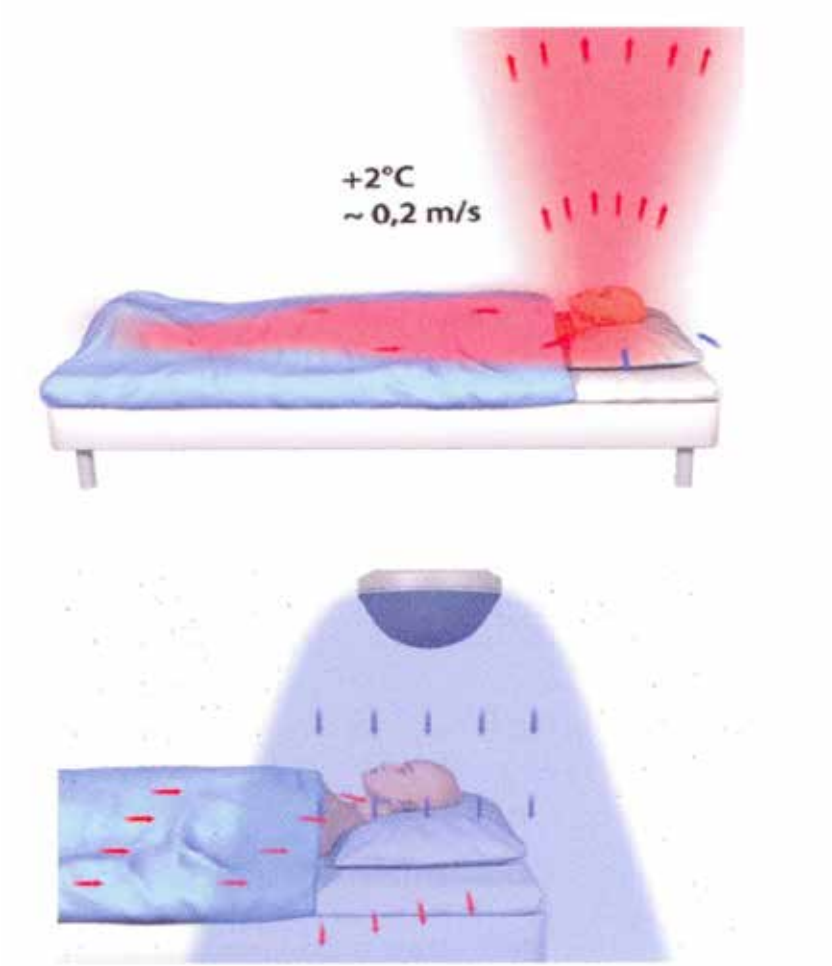

Figure 1 Allergen exposure at night time and the intervention of the laminar airflow.

Figure 2 Bed encasing for HDM avoidance.

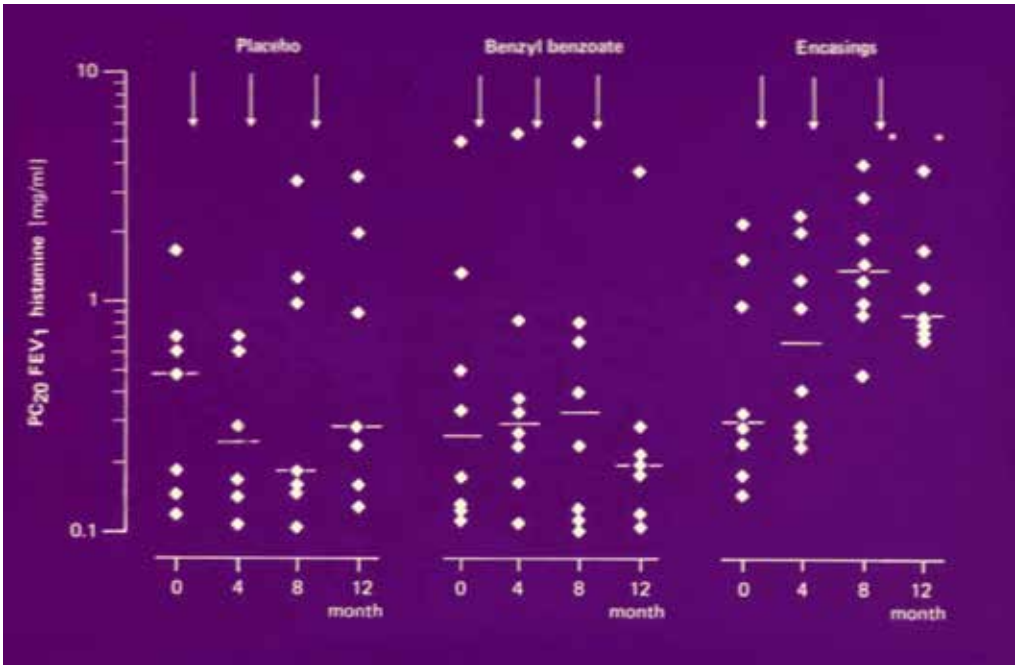

Figure 3 Comparison between bed encasing and acaricides.

gen exposure but to reduce broncho-hyperresponsiveness. More recently laminar airflow systems in connection with allergen filters have been shown to be useful for HDM allergic patients during the night, particularly in severe, uncontrolled asthma (figure 1).

TABLE 1

Strategies for elimination of indoor allergens
• Avoid furred pets (cats, dogs, guinea pigs, rats etc.)
• Reduce indoor humidity
• Improve ventilation
• Implement encasings for mattress and duvets/pillows
• Most acaricides (benzylbenzoate) are ineffective !
• Avoid wall-to-wall carpets
• Consider laminar airflow system

The elimination of moulds and their allergens obviously relates to indoor humidity. Strategies for elimination are currently not based on scientific evidence.

Avoidance of pet allergens has to do with avoidance of pets in the domestic environment. While exposure to allergens from cats may be relevant in kindergardens and schools, most children spend the majority of time indoors at home, so that elimination of domestic pets is still a reasonable recommendation for affected families. Realistically we have to assume that still relevant airborne concentrations from cats and other animals will remain in the domestic environments even months after elimination.

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2b AVOIDANCE MEASURES - FOCUS ON DIET

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KEY MESSAGES

- Food allergen avoidance in pregnancy, lactation and infancy has failed to prevent the development of allergic disease
- Food allergen consumption is necessary to establish the immune response leading to oral tolerance
- The only current recommendations to prevent allergic disease are exclusive breast-feeding at least 4 to 6 months and if breastfeeding is insufficient or not possible, hypoallergenic formula for high risk infants
- There is evidence consistent with the hypothesis that sensitisation to foods may occur via the cutaneous route
- Oral tolerance induction or improving skin barrier function may prevent the development of food allergy and other allergic diseases

Food allergy and other allergic diseases have become more prevalent in the past years. There is no clear evidence as to why this has occurred. Infantile eczema and food allergy are usually the first steps in the allergic march, followed later on by respiratory allergies, including asthma and allergic rhinitis. For many years, food allergen avoidance in pregnancy, lactation and infancy was recommended to prevent the development of food allergy, and possibly other allergic diseases, with the view that allergic sensitisation happens in the gastrointestinal tract and would not happen in the absence of gastrointestinal exposure. However, public health guidelines supporting allergen avoidance have failed to prevent the development of food allergies (Figure 1). This may be because allergen is required for the establishment of oral tolerance and/or because sensitisation does not occur via the gastrointestinal tract but via other routes.

The immune response leading to oral tolerance develops in the gut and requires the presence of food allergens. Other facilitating factors such as diverse gastrointestinal microbiome, and immunomodulatory factors in saliva and breast milk may also be necessary for the acquisition of tolerance. There is some observational evidence that initial sensitisation to food allergens occurs via the cutaneous route. For instance, early-onset severe eczema is associated with food allergy and topical exposure to peanut oil and high exposure to environmental peanut are associated with peanut allergy.

Currently, there are no clear guidelines other than recommending exclusive breast-feeding for the first 4-6 months of life and if breastfeeding is insufficient or not possible, hypoallergenic formula for high risk infants. Recent studies suggest that increased diversity of food within the first year of life might have a protective effect on asthma, food allergy, and food sensitization. Furthermore, early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. Randomised controlled studies looking at the impact of early introduction of allergenic foods on the prevalence of food allergy and other allergic diseases are underway.

If a food is consumed in a certain society and location, this results in both environmental and oral

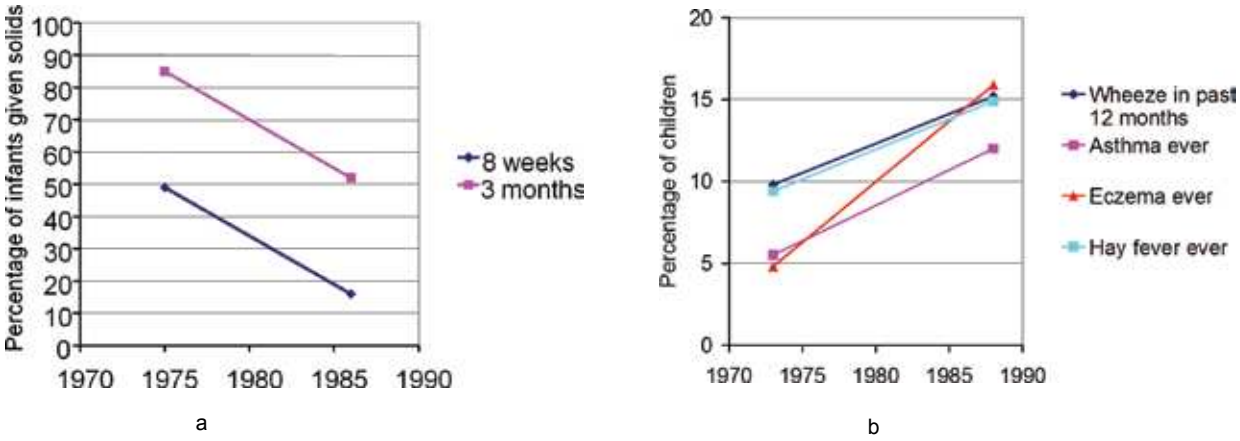

Figure 1 a - Change in commencing solids between 1975 and 1986; b - Change in the prevalence of allergic conditions in children in South Wales between 1973 and 1988.

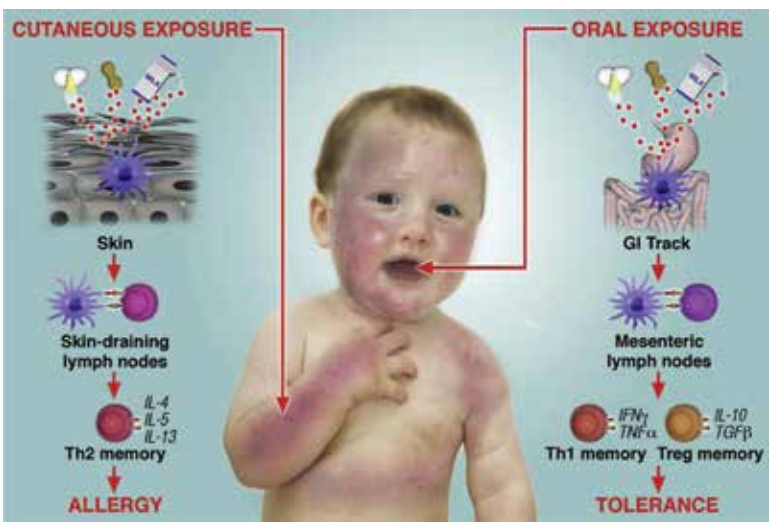

Figure 2 Dual-allergen exposure hypothesis for the pathogenesis of food allergy. Allergic sensitisation results from cutaneous exposure and tolerance occurs as a result of oral exposure to food. (*Reprinted from J Allergy Clin Immunol, 121/6, Lack G. Epidemiologic risks for food allergy, 1331-1336, Copyright 2008, with permission from Elsevier.*)

exposure (Figure 2). If in fact sensitisation occurs via the cutaneous route and oral tolerance occurs via the oral route, novel ways to prevent food allergy might include: oral tolerance induction both in high and low risk infants through early introduction of food, or improvement of the skin barrier.

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2c PERINATAL RISK FACTORS AND STRATEGIES FOR ALLERGY PREVENTION

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KEY MESSAGES

- Smoking is an avoidable risk factor that must be strongly discouraged at every age, particularly in pregnancy and childhood
- Breastfeeding is recommended for at least 6 months for many reasons, although the specific evidence for allergy prevention is not strong
- There is little evidence that avoiding allergenic foods or delaying the introduction of complementary solid foods reduces the risk of allergy
- Most importantly, there is ongoing research to explore the role of probiotic and prebiotic supplements to restore declining microbial diversity, and other immunomodulatory dietary nutrients such as polyunsaturated fatty acids, antioxidants, folate and vitamin D in allergy prevention – which may all reduce the risk of many other inflammatory non-communicable diseases

Modern environmental changes have had many adverse effects on human health, increasing the risk of many inflammatory non-communicable diseases (NCDs). Most of these chronic diseases of 'modern life' (including asthma, allergies, heart disease, diabetes and obesity) are associated with similar modern environmental risk factors. Allergy is the earliest onset NCD, often beginning in the first months of infancy and a clear indication that the developing immune system is particularly vulnerable to environmental change. In this regard, we can consider allergy as 'the canary in the coal mine'- a useful early barometer of environmental impact on human health (Figure 1). These environment-driven changes begin in pregnancy, with emergent differences in immune function detectable at birth for newborns, who go on to develop allergies (Figure 2).

Figure 1 A 'canary in the coal mine': Beginning in infancy allergy is the earliest onset NCD, and a sensitive early measure of the effects of the modern environment on immune health. (*Reproduced with permission from Prescott SL. Disease Prevention in the Age of Convergence - the Need for a Wider, Long Ranging and Collaborative Vision. Allergol Int 2014; 63:11-20.*)

Maternal diet, microbial exposures and toxic exposures in pregnancy are implicated in allergy and in many other NCDs, increasing the predisposition, sometimes many years later. These same risk factors have ongoing role in early childhood, influencing the balance of gut bacteria, and developing immune and metabolic responses, and the predisposition to both allergy and other NCDs (Figure 3).

The keys to prevent disease must, therefore lie in very early life before the onset of disease, and before allergic immune responses have become consolidated. Over the past decades, there has been a shift away from allergen avoidance strategies and towards more immunomodulatory approaches. This is because allergen exposure

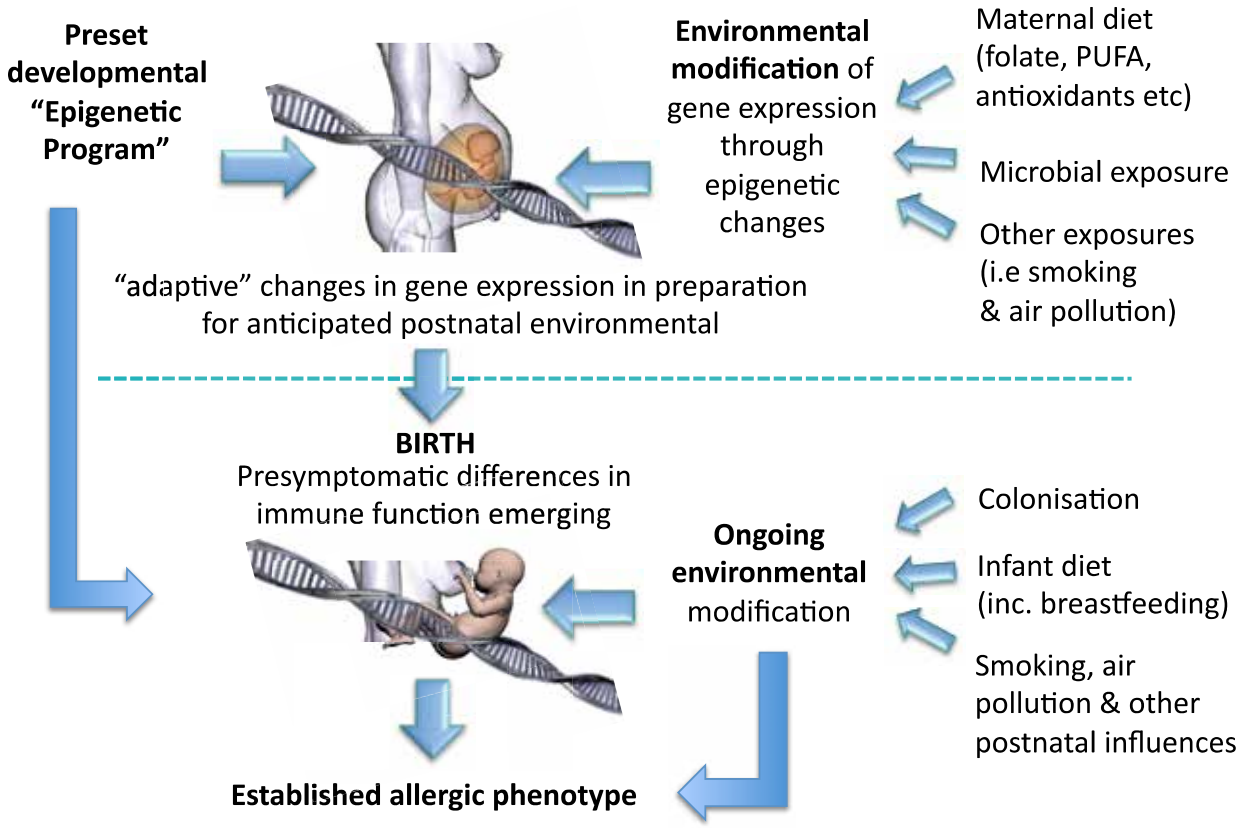


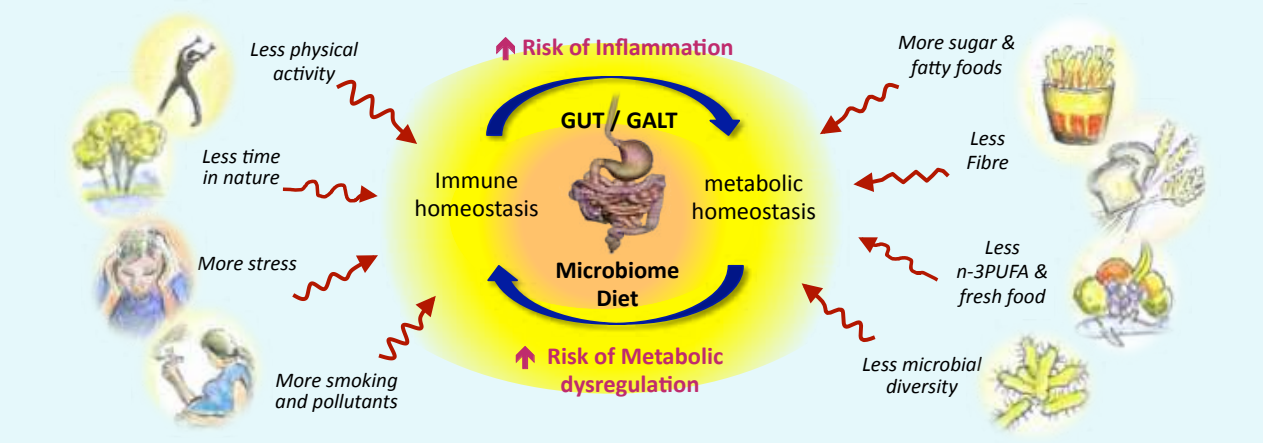
Figure 2 Maternal environmental exposures in pregnancy may influence many aspects of development through changes in fetal gene expression. Coupled with ongoing environmental exposures in the first months of life, this will influence the risk of early and late onset NCDs. (*Reproduced with permission from Martino D, Prescott SL. Silent mysteries: epigenetic paradigms could hold the key to conquering the epidemic of allergy and immune disease. Allergy 2010; 65:7-15, with permission from Willey Blackwell.*)

is unlikely to be driving the allergy epidemic, and there is little evidence that allergen avoidance in pregnancy, lactation or the infant diet plays any role in prevention of allergic disease. The optimal timing for introduction of allergenic foods for allergy prevention is still the subject of research trials. Based on the currently available evidence, most experts recommend introducing complementary solid foods from around 4-6 months, including potentially 'allergenic' foods. Breastfeeding is strongly encouraged, and there have been some suggestions that breastfeeding during the period that foods are first introduced may help prevent the development of allergy, although this is not proven.

A more promising and logical strategy to prevent disease is to target the background environmental risk factors (Figure 3) that appear to be driving the rising risk of allergy and other inflammatory diseases – beginning in early life (Figure 4). At present, there are a number of trials underway to explore the role of immunomodulatory factors such as prebiotics (soluble dietary fibre) and probiotics, which may restore more favorable gut colonisation for the optimal metabolic and immune maturation. Polyunsaturated fatty acids and other nutrients, such as antioxidants and vitamin D may also play a role in counteracting the rising propensity for allergy and inflammation. These strategies are likely to have benefits for not just allergies but all NCDs. Common risk factors will mean common solutions in overcoming the modern pandemic of NCDs, highlighting the need for cross-sector, interdisciplinary approaches.

Many lifestyle risk factors for NCDs promote inflammation

Many have *direct* effects on immune function



Targets for prevention strategies: multisystem benefits

Figure 3 Many of the modern environmental risk factors implicated in the rise in allergy and other NCDs have effects on both metabolic and immune development. These are all the logical targets for preventing disease. (*Reproduced with permission from Prescott SL. Disease Prevention in the Age of Convergence - the Need for a Wider, Long Ranging and Collaborative Vision. Allergol Int 2014; 63:11-20.*)

Figure 4 Early environmental exposures have lasting effects on may aspects of growth and development, and the most effective strategies for preventing disease must begin in early life. (*Reproduced with permission from Prescott SL. Disease Prevention in the Age of Convergence - the Need for a Wider, Long Ranging and Collaborative Vision. Allergol Int 2014; 63:11-20.*)

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3 PHARMACOLOGICAL TREATMENT OF ALLERGIC DISEASE

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Allergic diseases affect over 30% of the population with variable severity based upon allergen exposure and the degree of hypersensitivity. A variety of medications are utilized for symptomatic therapy. In general, the treatment should be tailored to the primary symptom or symptoms and to the severity of symptoms. Usually specific mediator inhibitors, such as antihistamines provide more rapid relief, but are less effective for chronic symptoms, such as congestion. The variability of allergic diseases, their phenotypes and multiple treatment options have resulted in several step management strategies (Table 1, Figures 1 and 2). Combination therapies are often utilized though efficacy data are sparse. As contrasted with allergen immunotherapy, pharmacologic therapy usually does not modify the long-term outcome of allergy, although there are some exceptions.

KEY MESSAGES

- A variety of medications are utilized for symptomatic therapy of allergic diseases, usually in step management strategies
- Different from allergen immunotherapy, pharmacologic therapy usually does not modify the long-term outcome of allergy
- Treatment should be tailored to the primary symptom and to the severity of symptoms
- The optimal utilization of pharmacologic therapies varies among regions and countries. This variance may reflect the reliance on subjectivity in the clinical assessment, the variability of disease phenotypes and varying preference of therapies in different populations
- The availability of multiple options is desirable to tailor therapy to the individual

ANTIHISTAMINES

Oral: Second-generation antihistamines are more selective for the primary histamine receptor than first-generation antihistamines, and fexofenadine has a very low central nervous system concentration. The result is a much lower risk of side effects for second-generation antihistamines, with a preference for these due to safety but not enhanced efficacy. Compared to first-generation anti-histamines, second-generation antihistamines have less anti-cholinergic effects and less effect on glandular secretions.

Topical: Intranasal or ocular antihistamines are probably more effective for nasal or ocular symptoms than oral antihistamines. The advantages include a more rapid onset of symptom relief and some benefit for congestion and possibly for inflammation. Allergic conjunctivitis will also improve with nasal antihistamine treatment, but a variety of topical, ocular antihistamines are more effective. Non-allergic rhinitis does not respond to oral antihistamines, but likely improves with nasal antihistamine therapy, primarily because of the benefit on congestion. Currently, available intranasal antihistamines result in mild sedation due to systemic absorption. Efficacy of nasal antihistamines is less than nasal corticosteroids, although some studies show the two therapies to be equivalent.

CORTICOSTEROIDS

Topical: Intranasal corticosteroids are the single most effective therapy for intermittent and persistent allergic rhinitis. The delayed onset of action makes the thera-

TABLE 1

Combination Therapy *	
Combination	**Therapeutic considerations**
Oral antihistamine + decongestant	More effective for nasal congestion than antihistamine alone
Oral antihistamine + leukotriene antagonist	May be more effective than either agent alone but less effective than nasal corticosteroid
Oral + topical antihistamine	No evidence of additive benefit, topical antihistamine may help congestion
Oral antihistamine + topical corticosteroid	No evidence of benefit of antihistamine added to topical corticosteroid, may relieve more effectively itching
INCS* + anticholinergic	Improves rhinorrhea more than either agent alone
Intranasal antihistamine + corticosteroid	Combination product more effective than either agent alone, inadequate data if both administered independently
INCS** + oral leukotriene antagonist	Inadequate data

** (Adapted from Wallace DV, Dykewicz MS et al, J Allergy Clin Immunol 2008);*
***INCS: intranasal corticosteroid*

py less appealing for intermittent use as would be typically utilized for intermittent rhinitis. Intranasal corticosteroids are superior to the combination of oral antihistamine and leukotriene antagonist. Nasal corticosteroids are effective with as needed use, but efficacy is greater with regular nasal application. Local side-effects are minimal and include nasal dryness and irritation and nasal bleeding. Rare reports of nasal septal perforation are in the literature, but this is very unlikely. There is systemic absorption of nasal corticosteroid as demonstrated with careful studies of growth in children. The magnitude of the systemic effects is small due to the low dose, but concerns of growth, glaucoma, cataracts and even bone loss are real, albeit limited in occurrence. Ocular topical corticosteroids are also very effective, but the side-effect concerns are significant with the potential to exacerbate viral infection of the eye, particularly herpetic keratitis, to increase intraocular pressure and to enhance the development of cataracts. Inhaled corticosteroids are the mainstay of asthma controller treatment and are recommended as first-line treatment (Figure 2). As with rhinitis their intermittent use is less proven. Local side effects include oral candidiasis and pharyngo-laryngeal irritation. As with the nasal steroids there is systemic absorption with the risk of side effects such as growth retardation, bone loss or osteoporosis, increased fragility of the skin and suppression of the adrenal gland. Topical application of corticosteroids on the skin is recommended as second-line treatment of atopic eczema or atopic contact dermatitis. The lowest strength controlling the symptoms should be used. The potential for skin atrophy exists whenever topical corticosteroids are used, even with low potency preparations. Skin atrophy, along with other undesirable side effects such as telangiectasia and striae, can very rarely appear within 2 to 3 days of starting daily application, the greatest potential occurring when the application is occluded, when highly potent corticosteroids are applied or when the preparation is applied to fragile skin. Risk depends on the strength of the corticosteroid, the length of application, the site treated, and the nature of the skin problem.

Systemic: Oral or parenteral corticosteroids are very effective for all of the symptoms of allergic diseases. Treatment with topical corticosteroids is preferable while systemic therapy is reserved for severe uncontrolled symptoms. Systemic corticosteroids have serious potential side-effects, which include sleep disturbance, mood change, appetite increase, glucose intolerance, aseptic bone necrosis, accelerated bone loss, increase in central body fat, and decrease in muscle strength. Due to the serious side-effect profile, systemic corticosteroids ideally should be limited to a brief period of time.

CROMONES

Sodium cromolyn is available for topical treatment of allergic rhinitis, asthma and conjunctivitis and limited benefit for food allergy and gastrointestinal mastocytosis. Since the action of the medication is to inhibit calcium fluxes in mast cells and basophils, the benefits generally are prevention of symptoms rather than relief of current or active symptoms. Thus, the optimal treatment is regular application during times of active symptoms or utilization prior to contact with known or suspected allergen. Cromones have an excellent safety profile with no known, significant side effects. The necessity for dosing multiple times a day markedly diminishes the effectiveness of these agents, and they are generally not cost effective and only modestly effective.

LEUKOTRIENE INHIBITORS

Oral leukotriene inhibitors improve the symptoms of allergic rhinitis and asthma. The combination of leukotriene inhibitors and

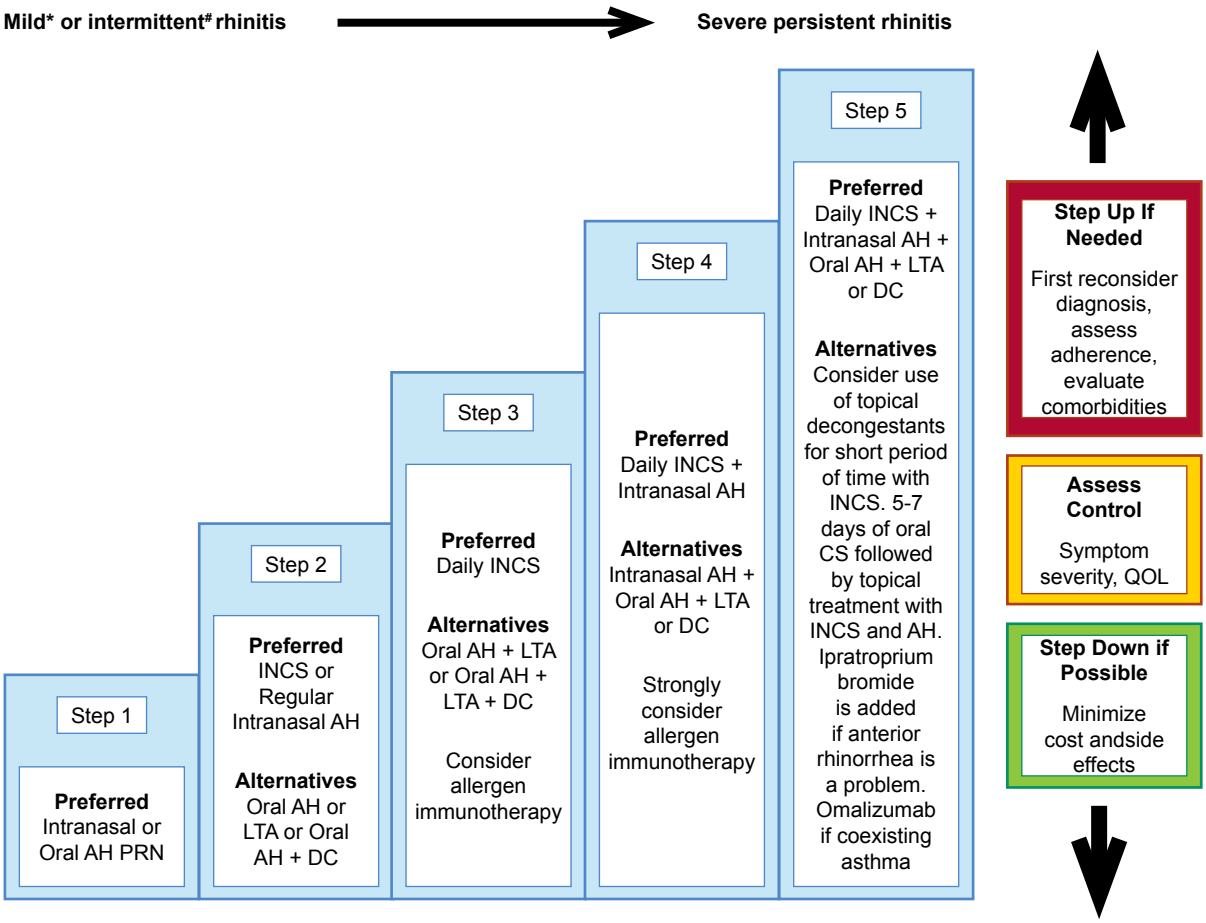

Figure 1 Treatment Steps in Allergic Rhinitis (adapted from Meltzer Allergy Asthma Proceedings 2013); # Intermittent is defined by ARIA as symptoms for 4 days or less a week or less than 4 consecutive weeks; * Mild indicates the absence of sleep disturbance, impairment of daily activities, impairment of school or work productivity. Symptoms are noted but not troublesome. AH: Antihistamines, PRN: As needed, LTA: Leukotriene antagonists, INCS: Intranasal topical corticosteroid, DC: Decongestant, CS: Corticosteroid, QOL: Quality of life.

oral antihistamines is not clearly superior to either agent alone. Leukotriene inhibitors are less effective for itching and sneezing than antihistamines, but are likely more effective for congestion and cough. Improvement of asthma, frequently associated with allergic rhinitis, is an advantage of oral montelukast therapy of rhinitis.

TOPICAL ANTICHOLINERGICS

Intranasal ipratroprium bromide relieves rhinorrhea but has no effect on other symptoms. The combination of nasal anticholinergic therapy and oral antihistamine is more effective than either agent alone. Recently inhaled long acting anticholinergics (tiotropium) were evaluated as add-on controller treatment for moderate/severe asthma and provided a similar efficacy profile to long-acting beta2 simpatomimetics (LABAs). There is no significant systemic side effects proven, although there have been questions raised about inhaled anticholinergic therapy increasing cardiovascular and cerebrovascular disease. This concern has not been confirmed in large studies of inhaled anticholinergic therapy for chronic obstructive lung disease but has been suggested by retrospective data.

TOPICAL BETA 2 SIMPATOMIMETICS

Inhaled short-acting beta2-simpatomimetics are used as reliever medication for asthma, while LABAs are recommended as add-on controller treatment when asthma is not controlled by inhaled corticosteroids alone. LABAs alone are contraindicated as single-agent controller for asthma due to the risk of increasing all cause mortality and asthma related severe adverse events.

ALTERNATIVE AND OPTIMIZED THERAPIES

Numerous pharmacologic agents

Asthma education. Environmental control. (If step-up treatment is being considered for poor symptom control, first check inhaler technique, check adherence, and confirm symptoms are due to asthma.)				
As needed rapid-acting β_2-agonist	As needed rapid-acting β_2-agonist			
Controller options***	Select one	Select one	To Step 3 treatment, select one or more	To Step 4 treatment, add either
	Low-dose inhaled ICS*	Low-dose ICS plus long-acting β_2-agonist	Medium-or high-dose ICS plus long-acting β_2-agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier**	Medium-or high-dose ICS Low-dose ICS plus leukotriene modifier	Leukotriene modifier Sustained release theophylline	Anti-IgE treatment
		Low-dose ICS plus sustained release theophylline		

* ICS = inhaled glucocorticosteroids
**= Receptor antagonist or synthesis inhibitors
*** = Recommended treatment (shaded boxes) based on group mean data. Individual patient needs, preferences, and circumstances (including costs) should be considered.

Figure 2 Treatment steps on asthma. Asthma medications are divided in relievers and controllers. The reliever medications must be prescribed in each step. The main controller medications are inhaled corticosteroids; long acting bronchodilators (β2 agonists) can be added when asthma is not adequately controlled with corticosteroids. When patients are not controlled with optimal doses of inhaled corticosteroids in combination with long acting β2 agonists, other adjunctive secondary controller medications might be considered. (*Reproduced from the Global Strategy for Asthma Management and Prevention, 2012 with permission of Global Initiative for Asthma (GINA)).*

have been tried topically and systemically for allergic diseases with variable results. Most of these target specific inflammatory mediators or pathways. The optimal utilization of pharmacologic therapies is outlined in various guidelines. These vary among regions and countries, and the assessment of the data in support of specific therapies is interpreted differently. This variance may reflect the reliance on subjectivity in the clinical assessment, the variability of disease phenotypes and specific allergens causing disease in different parts of the world, and varying preference of therapies in different populations. The availability of multiple, pharmacologic options is desirable to tailor therapy to the individual.

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4 ANTI IgE TREATMENT FOR ALLERGIC DISEASE

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KEY MESSAGES

- IgE-mediated allergic reactions can be prevented by selected antibodies against IgE that specifically bind and neutralize IgE in circulation
- Anti-IgE antibodies prevent IgE from interacting with high and low affinity IgE receptors on mast cells, basophils, B cells and certain antigen-presenting cells
- Therapeutic anti-IgE antibodies do not recognize Fc receptor (R)-bound IgE and thus are non-anaphylactogenic
- Omalizumab is registered for the treatment of moderate-severe allergic asthma, where it significantly reduces exacerbations and corticosteroid use and enhances quality of life
- Omalizumab has recently been approved for patients with chronic idiopathic urticaria/chronic spontaneous urticaria, who remain symptomatic despite H1 antihistamine treatment
- Omalizumab induces down-regulation of FcεRI on mast cells and basophils, inhibits IgE-mediated allergen-presentation by FcεRI-bearing antigen-presenting cells, and reduces IgE production after longer-term treatment
- Other applications of anti-IgE antibodies may include atopic dermatitis, food allergy, as an adjunct to allergen immunotherapy and allergic rhinitis

Immunoglobulin E (IgE) plays an important role in the pathophysiology of allergies and allergic asthma and IgE-mediated allergic reactions can be prevented by selected antibodies against IgE that specifically bind and neutralize IgE in circulation. Due to their epitope-specificity, selected anti-IgE antibodies prevent IgE from interacting with high affinity IgE receptors (FcεRI) on mast cells, basophils, and dendritic cells as well as with low-affinity IgE receptors (FcεRII/CD23) on B cells and certain antigen-presenting cells. Such therapeutic anti-IgE antibodies (e.g. Omalizumab) are directed against the region on IgE that is recognized by the two IgE receptors and therefore efficiently block IgE binding to these receptors, but do not recognize receptor bound IgE and thus are non-anaphylactogenic (Figure 1) .

Omalizumab is a humanized IgG1 monoclonal anti-IgE antibody that was approved by the US Food and Drug Administration (FDA) in 2003 for adults and adolescents with moderate-to-severe persistent allergic asthma, whose symptoms are inadequately controlled with inhaled corticosteroids. In the European Union, omalizumab is approved for the treatment of patients with severe persistent allergic asthma. Free IgE levels in serum of asthma patients decline rapidly after start of omalizumab therapy and because IgE bound to omalizumab cannot interact with IgE receptors, omalizumab is able to prevent the IgE-induced release of inflammatory mediators from mast cells and basophils without inducing degranulation. Subsequently, the allergic inflammation involving T cell and eosinophils and their inflammatory mediators is attenuated and beneficial effects on airway remodeling, (e.g. reduction of airway wall thickening), can be observed. Omalizumab also induces down-regulation of FcεRI on mast cells and basophils

TABLE 1

Effects of anti-IgE treatment (omalizumab) in patients with severe allergic asthma on clinical endpoints in a representative clinical study

	Omalizumab N=209	Placebo N=210
Severe asthma exacerbations		
Rate per 28-week period	0.24	0.48
% reduction, p-value for rate ratio	50.1%, p = 0.002	
Emergency visits		
Rate per 28-week period	0.24	0.43
% reduction, p-value for rate ratio	43.9%, p = 0.038	
Physician`s overall assessment of treatment effectiveness		
% excellent/good responders	60.5%	42.8%
p-value	<0.001	
Asthma Quality of Life		
% of patients ≥0.5 improvement	60.8%	47.8%
p-value	0.008	
Lung function (FEV1)		
Improvement after 28 week treatment	190 ml	96 ml
p-value	0.043	

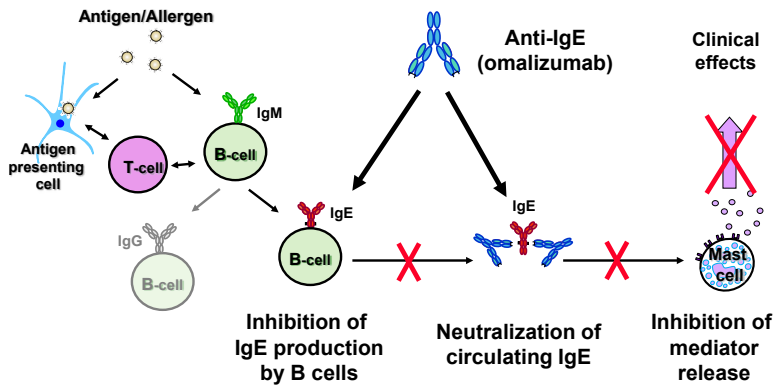

Figure 1 Mechanism of action of anti-IgE therapy.

(which is controlled by free IgE), inhibits IgE mediated allergen presentation by FcεRI bearing antigen presenting cells, and after longer-term treatment reduces IgE production (by interacting with surface IgE-positive B cells).

Omalizumab is administered as a subcutaneous injection every two or four weeks with a dose adjusted to body weight and serum IgE levels in order to guarantee sufficient neutralization of IgE and it is overall well tolerated.

The clinical efficacy of omalizumab in patients with moderate-to-severe and severe allergic asthma has been well documented in several large-scale clinical trials resulting in over 60% responders with reduction in exacerbations, reduction in corticosteroid use, and enhanced quality of life (Table 1). In addition, omalizumab has recently been approved for patients with chronic idiopathic urticaria/chronic spontaneous urticaria who remain symptomatic despite H1 antihistamine treatment, where it showed a fast response and a high response rate. Furthermore, omalizumab has been evaluated in a number of allergic diseases with reports of benefits e.g. in atopic dermatitis, seasonal and perennial allergic rhinitis, food allergies, and as an adjuct therapy for allergen immunotherapy .

Novel anti-IgE monoclonal antibodies with improved pharmacodynamic and immunomodulatory properties are under development.

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5 BIOLOGICAL AGENTS FOR THE TREATMENT OF ALLERGIC DISORDERS

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KEY MESSAGES

- Biological agents (biologicals or biologics) target a selected disease-inducing molecule
- In allergic disorders, several biologicals are being assessed in clinical trials, including biologicals inhibiting interleukin (IL)-4, IL-5, IL-9, IL-13, and immunoglobulin E
- Most of these biologicals are still being tested in clinical trials, involving patients with allergic asthma, allergic rhinitis, food allergy, urticaria, atopic eczema, and diseases with high eosinophil counts
- It is to be expected that biologicals will replace or reduce the use of the currently prescribed unspecific pharmacotherapy of allergic inflammation
- Research on better understanding disease endotypes, identification of novel biomarkers and discovery of novel biologicals are developing in parallel

In recent years, scientists have exploited the immune system to produce antibodies from single B cell clones, heralding the era of monoclonal antibodies (Figures 1 and 2). Biological agents (biologicals or biologics) have revolutionized the treatment of many rheumatic and immunological disorders and are currently being assessed for allergic disorders.

Better understanding the endotypes and phenotypes of allergic disease may lead to specifically targeting the responsible molecular mechanism by a biological (Figure 3). Unlike traditional therapies of allergy, biologicals target a single molecule. Thus, the use of an anti-allergic biological ideally leads to the inhibition of a specific molecule involved in allergic inflammation, without weakening immunity against viruses and bacteria. The design and use of biologicals requires a profound understanding of the mechanisms underlying allergy.

Allergy is thought to arise as an aberrant immune response to one or more innocuous environmental allergens, such as pollen, food, house dust mites, insects or animal products. Such encounter with an allergen results in the activation of immune cells, such as type-2 T helper lymphocytes (TH2 cells) that become stimulated and produce cytokines, including interleukin-4 (IL-4), IL-5, IL-9, and IL-13 (Figure 3). Concomitantly, B lymphocytes are activated by the allergen and under the influence of TH2 cell-derived cytokines produce immunoglobulin E (IgE). Moreover, TH2 cell-derived cytokines activate other immune cells, including eosinophils, mast cells, and basophils, which all promote allergy. Biologicals target for example IL-4, IL-5, IL-13 or IgE.

Some of the biologicals targeting IL-4 appeared to show some benefit in subgroups of patients with allergic asthma, while not causing any of the unwanted effects of conventional asthma treatments. Currently, IL-4 and IL-13-targeting biologicals are under development and need further clinical trials with larger patient collectives and longer study durations. Similarly, biologicals targeting IL-5 appeared to be beneficial in a subgroup of asthma patients characterized by the presence of high counts of eosinophils. Such

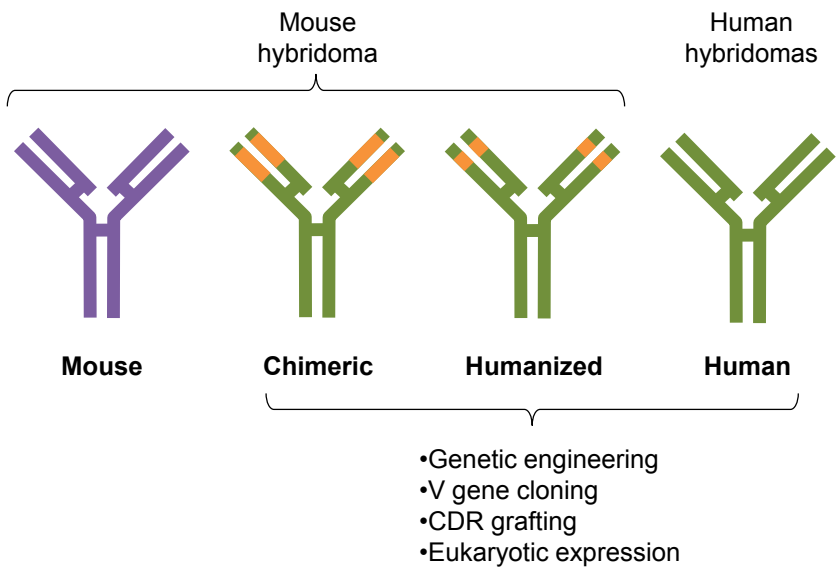

Figure 1 Several technologies are applied to produce monoclonal antibodies. (*Reprinted from J Allergy Clin Immunol, 130/Ballow M, Akdis CA, Casale TB, Wardlaw AJ, Wenzel SE, Ballas Z, et al. Immune response modifiers in the treatment of asthma: A PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology, 311-24. Copyright 2012, with permission from Elsevier.*)

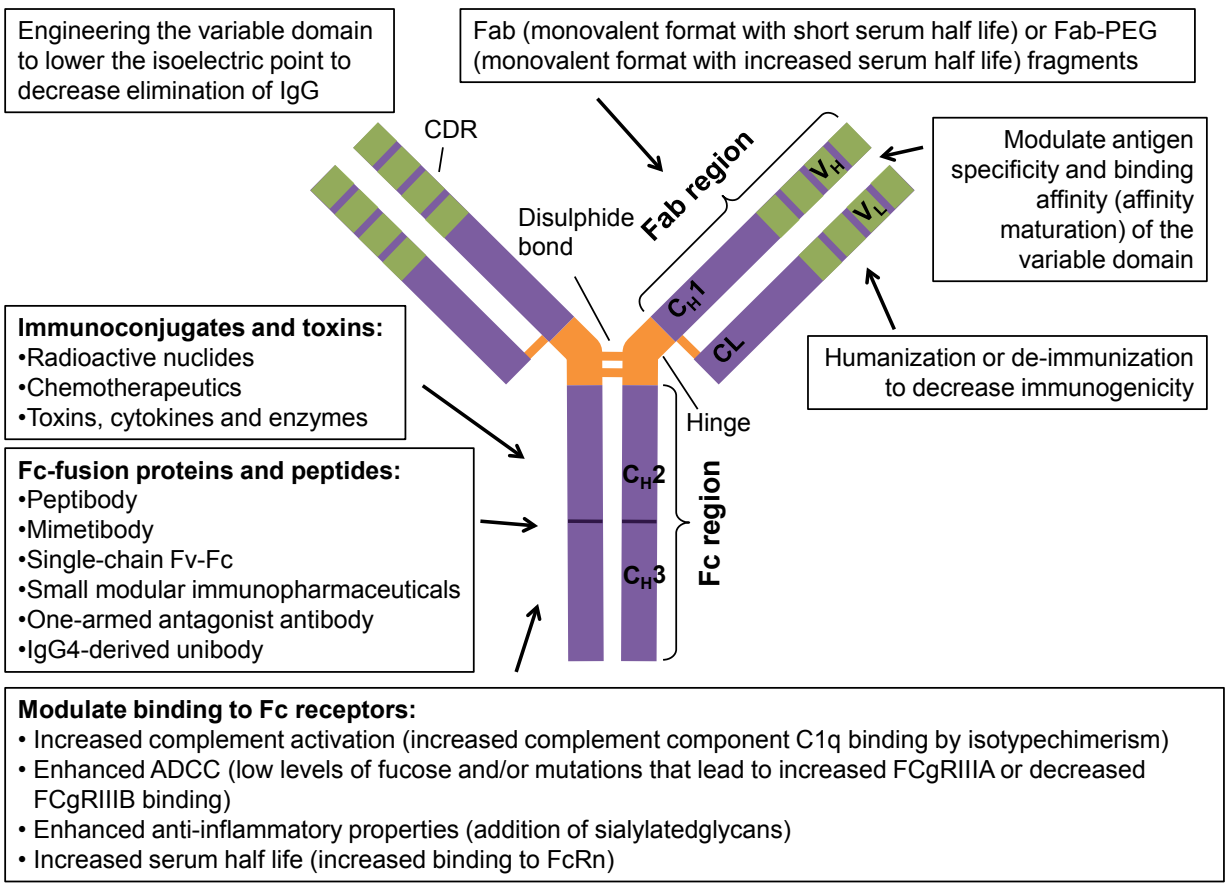

Figure 2 Modifications of the Ig molecule in order to engance its pharmacological and clinical potency. (*Reprinted from J Allergy Clin Immunol, 130/Ballow M, Akdis CA, Casale TB, Wardlaw AJ, Wenzel SE, Ballas Z, et al. Immune response modifiers in the treatment of asthma: A PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology, 311-24. Copyright 2012, with permission from Elsevier.*)

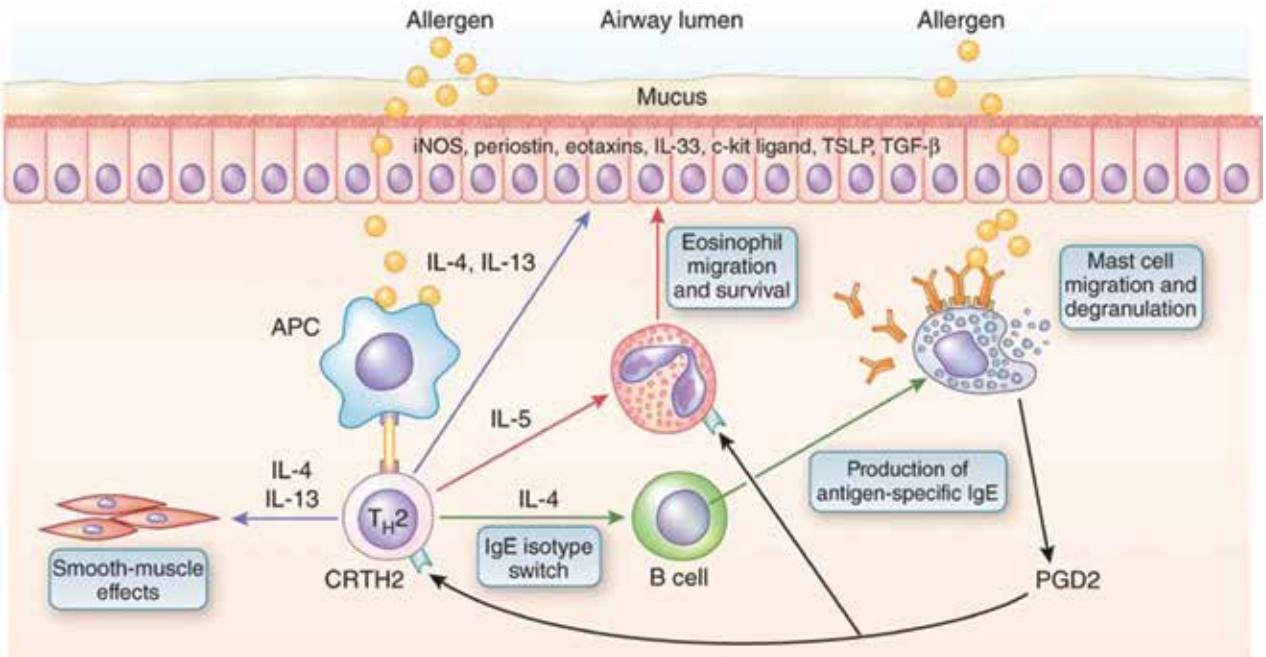

Figure 3 T_H2 immune processes in the airways of asthmatic patients. The pathway begins with the development of T_H2 cells and their production of the cytokines IL-4, IL-5 and IL-13. These cytokines stimulate allergic and eosinophilic inflammation as well as epithelial and smooth-muscle changes that contribute to asthma pathobiology. APC, antigen-presenting cell; CRTH2, chemoattractant receptor-homologous molecule expressed on T_H2 cells; iNOS, induced nitric oxide synthase; PGD2, prostaglandin D2; TSLP, thymic stromal lymphoprotein. (*Reprinted by permission from Macmillan Publishers Ltd: Nat Med, Wenzel SE, Asthma phenotypes: the evolution from clinical to molecular approaches, 18,716-25, copyright 2012.*)

considerations also apply to an IL-13-targeting biological, since asthma patients with high serum periostin levels responded best to this drug.

Moreover, IL-4-targeting biologicals are being tested in patients with allergic eczema, while biologicals blocking IL-5 are being assessed in allergic disorders characterized by increased counts of eosinophils, such as eosinophilic esophagitis and allergic nasal polyposis. Also, certain subtypes of urticaria might be amenable to biologicals inhibiting IL-1.

While the use of biologicals in allergic disorders is - for most of the biologicals - still in its infancy, biologicals have already changed the therapy of many rheumatic and immunological diseases. It is to be expected that the treatment of allergic disorders will shift from the use of unspecific drugs to biologicals.

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6 BIOSIMILARS AND ALLERGY TREATMENT

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Globally, a large number of blockbuster biotherapeutic molecules will go off patent in the next few years. This will change the scenario of allergy/clinical immunology and asthma treatments. There is a growth of generic drugs for the mass target therapy, accounting for the majority of patients (at least two/thirds as far as asthma is concerned) . Generic drugs have and will be developed to reduce the cost of asthma treatment, although this will be complicated by potential change of the used device/inhaler (Figure 1).

On the other hand, a smaller proportion of patients will require personalized (or in most cases phenotype driven) therapy. The real need for a cost/effective approach of this last treatment is the paucity of predictive biomarkers of response (if any exist up to now). These last patients are candidate to biologic treaments, mainly with monoclonal antibodies, however with a high cost. So, as for the "old" blockbusters, there is a need nowadays to reduce expenses/costs for biologic treatments, mainly in chronic diseases (as already in many immunological diseases). A new opportunity in this sense is provided by the biosimilars.

KEY MESSAGES

- A large number of blockbuster biotherapeutic molecules for allergic diseases and asthma are going off patent in the next few years
- There is a need to adjust medication costs to low-income markets
- Allergy and asthma treatment will dramatically change in the next decade. A great part of patients will use pharma treatments (generics or branded drugs) whereas a minority will need biologic treatmens (branded or biosimilars)
- Biosimilars are approved through an abbreviated route, which relies on limited safety and efficacy data. The cost is ten time less and the process to reach the market is shortened by 50%
- Biosimilars offer a good opportunity to reduce costs for biologic treatments

THE DEFINITION OF BIOSIMILAR

Similar Biological Medicinal Product (EMA)

Follow-on Protein Product (FDA)

Subsequent Entry Biologic (Health Canada)

Follow-on Biologic (Japan)

In the European Community (EC), a copy which is claimed to be 'similar' to a reference medicinal product, which has been granted a marketing authorization (MA) within the EC is defined 'similar biological medicinal product' or 'biosimilar'. European Medicine Agency (EMA) approved the first biosimilar product in 2006. The first "Guidelines on Biosimilars" have been released by EMA, and thus EC and EMA are leaders in the concept of biosimilars in the world.

DEVELOPMENT AND PRODUCTION OF BIOSIMILARS

Unlike generics, biosimilars are similar, but not identical to their reference products, because their chimical characteristics are directly related to the manufacturing process, which cannot be precisely duplicated. Thus, biosimilars require an approach to grant the MA, different from both originators

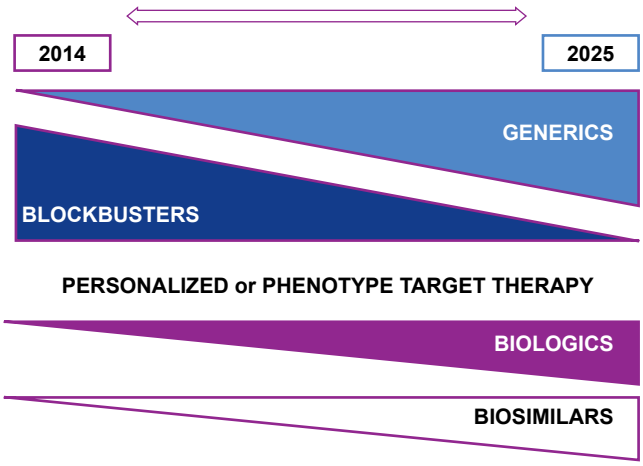

Figure 1 The future scenario of allergy and asthma treatment will dramatically change in the next decade. A great part of patients will use pharma treatments(generics or branded drugs) whereas a minority will need biologic treatmens (branded or biosimilars).

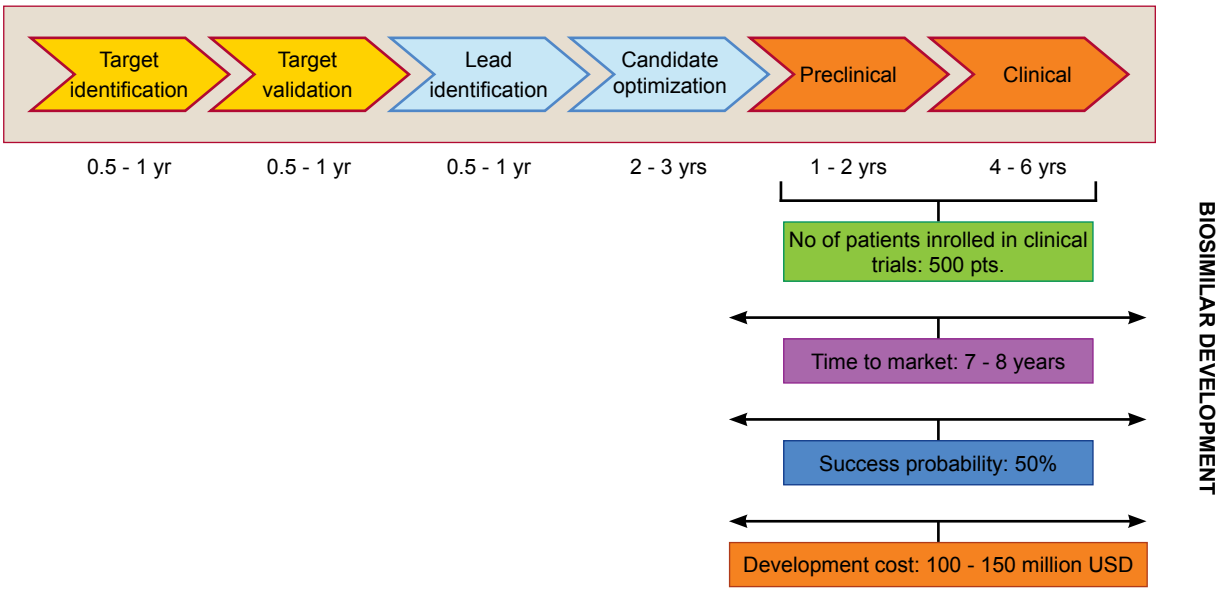

Figure 2 The development of a biosimilars is much less expensive (1 log less) then the reference biologic product. This allows to commercialize the biosimilars with reduced costs.

and generics. Nonetheless, these products are approved through an abbreviated route, which relies on limited safety and efficacy data (Figure 2). The cost to reach MA for biosimilars is ten time less then the cost for the reference biologic compound. In addition, the process to reach the market has been shortened to half of the required time. For emerging economies, it is imperative to be able to provide safe and cost effective drugs for their huge, non-insured and poor population. The use of biosimilars will offer more opportunities to treat our patients at a reduced cost, making these expensive therapies more accessible.

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7 TARGETING BASOPHILS AND MAST CELLS FOR NOVEL TREATMENT APPROACHES

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The important role of basophils and mast cells in allergy has prompted intensive research in ways to inhibit their activation (Figures 1, 2). Four different approaches listed below are being pursued (Figure 3):

- Limiting the interaction between IgE and its high affinity Fc receptor (FcεRI)
- Activation of inhibitory receptors
- Specific inhibitors of cellular activation
- Reducing the function of basophils and mast cells during allergen immunotherapy

KEY MESSAGES

- Basophils and mast cells are important target cells for treatment of allergic diseases
- Activation of basophils and mast cells by allergens can be diminished by interfering in IgE binding to the high affinity Fc receptor for IgE
- During allergy immunotherapy basophil and mast cells activity is diminished due to direct and indirect effects
- Stimulus secretion coupling in basophils and mast cells can be altered by activation of inhibitory receptors and selective inhibitors of activation pathways

LIMITING THE INTERACTION BETWEEN IGE AND ITS HIGH AFFINITY FC RECEPTOR (FCεRI)

Multiple approaches have been initiated to limit the interaction of allergens with IgE and IgE with FcεRI on mast cells and basophils to diminish their activation in allergy. Small oligonucleotide aptamers, phage display-selected peptides, anti-IgE antibodies, anti-FcεRI antibodies and designed ankyrin repeat proteins (DARPins) have been developed to block IgE receptor binding.

Of these only the humanized anti-IgE antibody omalizumab is available for treatment. The effect of omalizaumab is limited, because it only depletes free IgE and cannot remove IgE from the basophil and mast cell membrane. It was shown that in skin mast cell response to allergen is hardly affected within 2 months, whereas basophils responses are diminished within a week, probably due to the short half-life of basophils.

Interesting novel developments are DARPins, which can actively promote the dissociation of IgE from FcεRI on basophils and mast cells within hours and in this way make these cells quickly insensitive for allergens.

ACTIVATION OF INHIBITORY RECEPTORS

A large number of immune inhibitory receptors have been described in immunology, including on basophils and mast cells. These receptors have the potential to down-regulate FcεRI-induced mast cell and basophil activation. Many of these receptors signal through the so-called immunoreceptor tyrosine-based inhibition motifs (ITIM) which selectively block the FcεRI-induced immunoreceptor tyrosine-based activation motifs (ITAM). One of these ITIM coupled receptors is FcγRIIB (CD32b), that has already been used as a target for potential treatments with fusion proteins. These

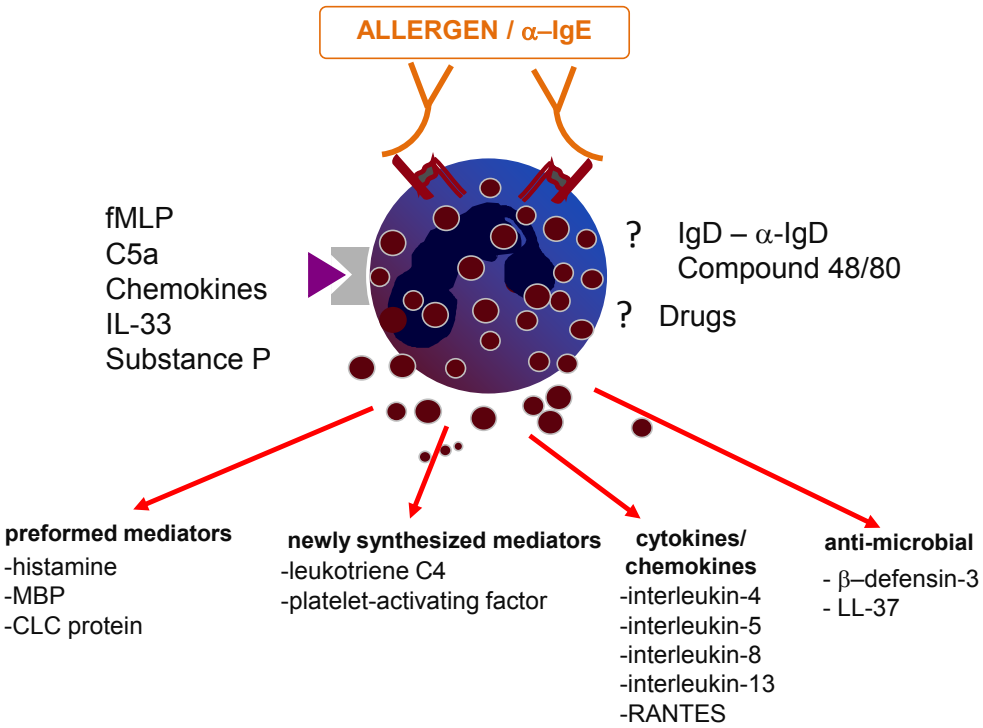

Figure 1 Basophils and mast cells activation by different type of stimuli. The most prominent activation is via allergen interactions with IgE causing crosslinking of FcεRI. Also other ligands can stimulate the cells via binding to specific receptors. For other triggers activators receptors are not completely clear. Activation of basophils and mast cells results in release of several types of mediators and cytokines/chemokines that are important in allergic diseases.

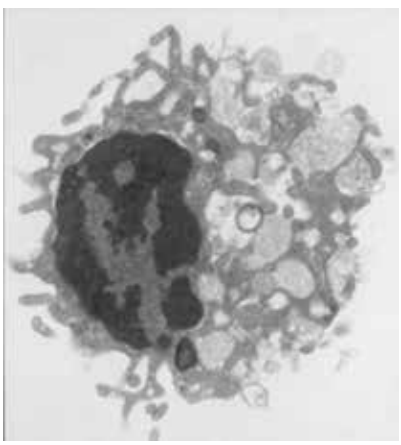

Figure 2 Degranulated human basophil. Electron microscopic photograph of an activated human basophil. Magnification 19,600 times.

studies showed that fusion proteins that co-aggregate FcγRIIB with FcεRI could be effective as novel drug candidates to prevent and treat allergic diseases. However, a clinical trial with an allergen-CD32b conjugate has been stopped due to unknown reason.

Other inhibitory receptors functionally described on basophils and mast cells are CD200R, CD300a, Leukocyte immunoglobulin-like receptor (LIR) family, CD84, SIRP-a, Siglecs, MAFA (not expressed on human basophils), Allergin-1 and LAIR-1/CD305. These families of inhibitory receptors include potent novel treatment modalities, but since these are not specific for basophils and mast cells it is a prerequisite to associate specific mast cell/basophil targeting strategies.

EFFECT OF SPECIFIC INHIBITORS ON CELLULAR ACTIVATION

Several compounds that are already in clinic do inhibit mast cell and basophil activation. A group of these drugs increase cellular cyclic AMP level via inhibiting phosphodiesterases, such as theophylline and 3-isobutyl-1-methyl-xanthine, siguazodan and rolipram.

Although many NSAID potentially increase basophil and mast cell activation, nimesulide is a chemically unrelated NSAID that inhibits both cell types. Glucocorticosteroids, known for their anti-inflammatory activities, also inhibit basophil, but not mast cell, activation. Calcineurin inhibitors, such as cyclosporine A and FK-506 also inhibit basophil and mast cell activation, including inhibiting the synthesis of IL-4 and

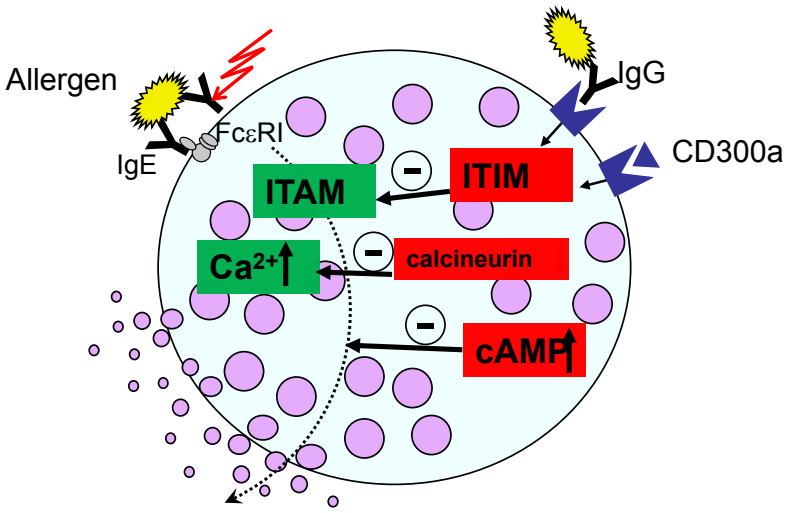

Figure 3 Allergen-induced activation of basophils and mast cells can be inhibited via different ways. The signal triggered by crosslinking of IgE by the allergen can be inhibited by reducing IgE bound to the FcεRI, but also by blocking its downstream signalling by specific inhibitors. The inhibitors are depicted in red, whereas the positive signals are in green. Allergen-specific IgG induced after AIT can bind to the FcγRIIb blocking receptor. Calcineurin inhibitors, such as cyclosporine, block the calcium signalling, whereas increased cAMP, after inhibiting phosphodiesterases reduces activation.

Il-13 in basophils.

There is much interest in implication of specific signal-transduction cascade inhibitors that will block the signalling after activation of the FcεRI by allergens. In vitro experiments have described potent inhibition by inhibiting PI3-kinase, protein kinase C or tyrosine kinases such as Lyn, Syk and Zap-70. Very potent and specific inhibitors for this pathway have been described, but since these signalling molecules are not specific for basophils and mast cells signalling, application in clinical studies is a challenge.

REDUCING BASOPHILS AND MAST CELLS FUNCTION FOLLOWING ALLERGEN IMMUNOTHERAPY

The only curative treatment in allergy is allergen immunotherapy (AIT). Several immunological mechanisms are supposed to explain this effect; changes on T helper cells and induction of regulatory T cells, the release of IL-10 and the synthesis of allergen-specific IgG and IgG4.

Although some studies have indicated that IL-10 can inhibit mast cells this is probably not its most likely effect with IgGs physically blocking allergen to reach IgE on basophils and mast cells more likely to support the effect. In addition, the IgG loaded allergens might still reach IgE on mast cells, but via simultaneous interaction with the FcγRIIb the activation will be diminished.

Analysis of basophils during AIT have shown release of inhibitory factors in the plasma. Basophils responses to FcεRI signalling were diminished following oral AIT for peanut allergy, which seemes like an anergic type of response.

Further research in AIT is focused on the development of allergen preparations that do not activate basophils or mast cells, while leaving T cell activation intact.

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8 TOLERANCE INDUCTION: PRINCIPLE AND MODALITIES

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KEY MESSAGES

- Immune tolerance is the lack of immune responsiveness to self-antigens, and harmless environmental antigens such as allergens
- There are two major pathways of immune tolerance, central and peripheral tolerance, which prevent immunity to self-antigens during lymphocyte development, and environmental antigens, respectively
- Regulatory T cells play a central role in peripheral tolerance, inhibiting effector pathways that drive allergic reactions, including allergen-specific Th2 and IgE responses, as well as cells that mediate allergic reactions such as mast cells and eosinophils
- Therapies such as allergen immunotherapy enhance regulatory T cell function to restore immune tolerance
- Regulatory B cells and immune regulatory subsets of other cells may play roles in immune tolerance to allergens

Immune tolerance is the unresponsiveness of the immune system to substances, cells and tissues that elicit an immune response (antigens). It prevents inappropriate immune responses to "self-antigens" present in the body's own tissues, which cause autoimmune disease, and reactivity to harmless environmental antigens. Lack of immune tolerance to allergens (e.g. grass pollen, cat dander and house dust mites) can lead to allergic disease.

Two major pathways of immune tolerance exist. During **central tolerance** immune cells (T and B lymphocytes) learn to discriminate self from non-self during development in the thymus and bone marrow respectively. Lymphocytes that recognise self-antigens are either eliminated (deleted) or rendered harmless (e.g. B cell receptor editing).

Peripheral tolerance develops after T and B lymphocytes mature and enter the periphery, and results in the lack of reactivity to environmental antigens. One important mechanism is through the induction of hyporesponsiveness (anergy) in T lymphocytes that encounter antigen in the presence of inhibitory signals or the absence of co-stimulatory signals that accompany inflammation. This leads to peripherally induced regulatory T (Treg) cells, which suppress inappropriate immune responses through cell contact-dependent and -independent mechanisms (Figure 1). Treg cells are essential to inhibit immune pathways and cells that cause allergic disease, including Th2-mediated inflammation, allergen-specific IgE, mast cells, and eosinophils (Figure 2).

A major Treg cell subset important in allergy expresses the transcription factor Foxp3. Young boys with a rare, X-linked, genetic mutation leading to the loss of Foxp3+ Treg (IPEX syndrome), suffer from multisystem autoimmunity, and symptoms of severe atopy including eczema, food allergy, and eosinophilic inflammation, highlighting the role of this subset in preventing allergic disease.

A second important T reg population expresses the anti-inflammatory mediator interleukin 10 (IL-10). Blood cells from non-allergic individuals stimulated with allergen in the laboratory make significantly more IL-10 than cells from allergic patients. Individuals with severe allergic and asthmatic

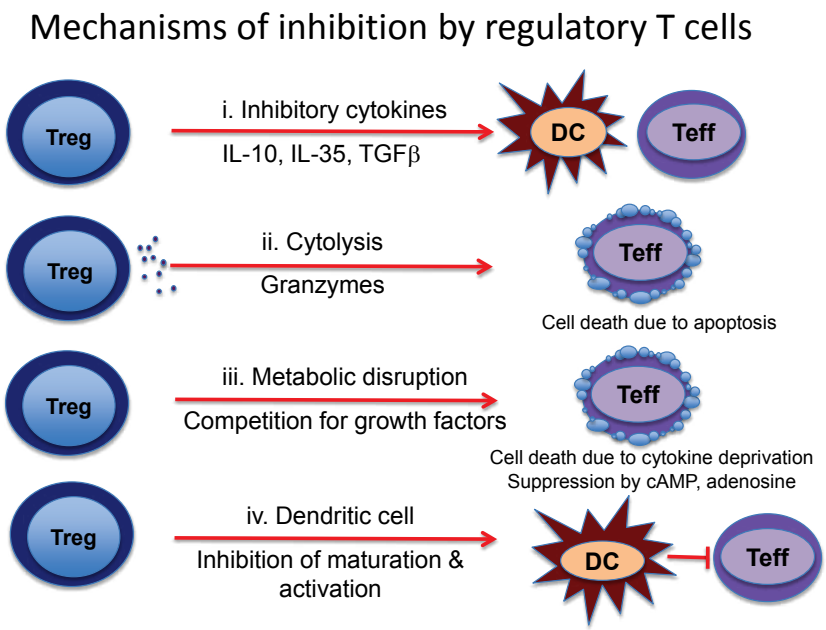

Figure 1 Regulatory T cells (Treg) inhibit immune responses by (i) release of inhibitory cytokines that suppress dendritic cell (DC) and effector T cell (Teff) functions, (ii) the synthesis of granzymes that cause apoptotic cell death, (iii) metabolic disruption by competition for essential growth factors such as IL-2, through constitutive expression of the high affinity IL-2 receptor (CD25), resulting in cell death; cyclic AMP (cAMP)-mediated inhibition, and CD39/CD73-generated, adenosine–mediated immunosuppression; (iv) interaction with DC to promote a tolerogenic phenotype, inhibit pro-inflammatory cytokine release, enhance IL-10 and inhibit Teff activation.

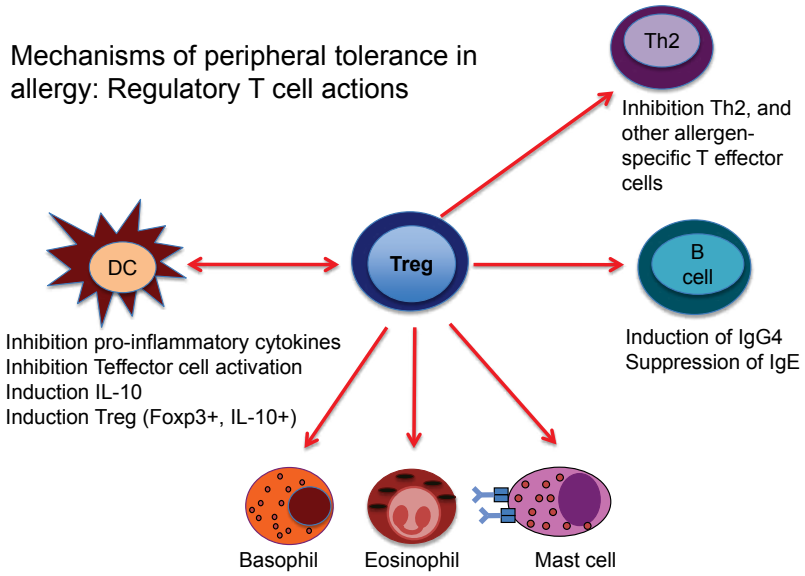

Figure 2 Treg act at multiple levels of the allergic cascade to prevent and control disease: induction of tolerogenic DC, which prevent allergen-specific Teff activation, and promote Foxp3+ and IL-10+ Treg; inhibition of Teff migration to tissues and suppression of Teff activation, including Th2 cytokine secretion; decreased IgE and enhanced IgG4 production by B lymphocyes; suppression of mast cell, basophil and eosinophil activation and degranulation. Treg are induced by AIT to mediate many of these actions, however other therapies may also promote immune tolerance.

disease show reduced IL-10 synthesis.

Because peripheral tolerance develops as a result of exposure to environmental antigens it is amenable to therapeutic manipulation. The best example is allergen immunotherapy (AIT), which involves administering increasing doses of allergen to the patient in order to induce allergen-specific long-term immune tolerance. AIT increases Treg particularly those that synthesize IL-10. Considerable research efforts are ongoing, including initiatives to identify adjuvants that can be used in conjunction with AIT, to improve its safety and efficacy.

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9a

ALLERGEN IMMUNOTHERAPY-OVERVIEW

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KEY MESSAGES

- Allergen immunotherapy (AIT) induces allergen-specific immune tolerance
- In contrast to pharmacotherapy, the effects of AIT persist after discontinuation and include prevention of new allergen sensitivities or progression to asthma
- AIT significantly improves in symptoms, medication use, and quality of life and is cost-effective compared to pharmacotherapy alone
- The two most commonly prescribed AIT routes are subcutaneous (SCIT) and sublingual (SLIT), with comparable efficacy; SLIT has a superior safety profile
- Adherence is equally poor with both routes and comparable with the low adherence seen with long-term pharmacotherapy

Allergen immunotherapy (AIT) is unique in that it treats both the symptoms of the allergic disease and its underlying cause by inducing allergen-specific immune tolerance. Numerous randomized-controlled trials have demonstrated significant improvement in symptoms, medication use, and quality of life with AIT in both asthma and allergic rhinitis patients. In contrast to pharmacotherapy, the treatment effects of AIT persist after discontinuation and include prevention of new allergen sensitivities or progression to asthma. AIT has also been associated with significant long-term and during treatment cost-savings compared with pharmacotherapy alone.

Globally, the two most commonly prescribed AIT routes are subcutaneous (SCIT) and sublingual (SLIT). The efficacy of these 2 routes appears comparable, with most double-blind, placebo controlled trials demonstrating an approximate 30% greater improvement in combined symptom-medication score compared with placebo (Table 1). Greater magnitudes of improvements have been seen in more symptomatic patient populations.

Adverse reactions associated with SCIT include local reactions, which are usually induration and erythema at the injection site and systemic reactions (SR). Systemic reactions, which occur at a frequency of about 0.1 % of injections, are generally mild (grade 1 or 2), but could potentially be life-threatening or fatal.

Because of potential for serious systemic reactions, it is recommended that SCIT be administered in a medically supervised setting with an appropriate wait-period after the injection. The safety profile with SLIT is more favorable than SCIT, which allows for home administration. Local reactions, such as oromucosal pruritus, are very common with SLIT, affecting up to 75% of patients. Local reactions usually occur during the beginning of treatment and resolve within a few days or weeks without any medical intervention such as dose adjustment, or premedication.

Which route is prescribed depends on a number of factors, including but not limited to, allergenic extract availability, geographic location of physician/patient, patient preference and ability to adhere with the particular regimen. With SCIT the treatment regimen requires frequent - usually weekly - visits during the initial updosing

TABLE 1

Comparison between different AIT regimens

Formulation	Regimen	Efficacy	Safety	Other
SCIT with unmodified extracts	Weekly updosing followed by 3 to 5 years monthly maintenance	~20-30% in CMS over placebo*	~0.1 % per injection SR	Premature discontinuation rates:** 6-84%
SLIT	Both no updosing and updosing schedules, most use daily maintenance for 3 to 5 years	~20-30% in CMS over placebo*	Oromucosal reactions common, SR rate : 0.056% per dose	Premature discontinuation rates: 21 to 93%
Intralymphatic	3 injections administered one month apart	Per nasal challenge more effective than placebo	No systemic reaction, local site reactions common	Efficacy comparable to 3 years of SCIT in open study
	3 and 6 injections administered at "minimum 14 days" apart	Per DBPC not more effective than placebo(5)	1/38 withdrew due to adverse effects	
Epicutaneous	6 weekly patches worn for 8 hours	30% improvement in VAS vs. placebo	11% discontinued treatment due to SR, local site eczema reactions common	
T-cell peptide (cat)	4 injections administered over 4 months	Nasal challenge TRSS 66% greater than placebo	Safety events: no difference from placebo	Efficacy maintained for ~ 2 years after treatment started
Modified SCIT (MATA MPL®) ¥ Ragweed and Grass	4 injection administered 7 days apart	Ragweed ECC: 48% improvement in TSS vs. placebo	Most AE local reaction injection site, 5/95 severe local reaction	
		Grass pollen season: 13.6% improvement in CMS vs placebo	Local reactions common, 1/514 severe SR in MATA MPL-erythema	Greater efficacy in subgroup analysis: more severe symptoms; 17%, >35 years disease duration; 31%

Abbreviations: CMS: combined symptom –medication scores, VAS: visual analogue score, SR: systemic reaction, TRSS: total rhinitis symptoms score, TSS total symptoms scores (nasal plus non-nasal symptoms)

**Range of efficacy reported but generally between 20-30% greater than placebo with greater effect seen in more symptomatic patients*

Premature discontinuation defined differently in various studies but generally defined as stopped without physician authorisation or < 2 or 3 years

¥ MATA MPL is a preparation containing pollen allergoid adsorbed onto tyrosine and with the adjuvant monophosphoryl lipid A (MPL).

phase. This is followed by a maintenance phase, during which the injections are administered at monthly intervals. Many SLIT regimens require no updosing and the need for an updosing phase has not been clearly established. The maintenance dosing frequency for SLIT is usually daily. Both routes require multi-year treatment (usually 3 to 5 years).

Adherence is equally poor with both routes and comparable with the low adherence seen with long-term pharmacotherapy. Interventions such as more frequent clinic monitoring, telecommunication reminders and educational programs may improve adherence.

Efforts to improve AIT has resulted in some promising developments such as modified allergens, T-cell peptides, adjuvants and alternate routes (intralymphatic or epicutaneous) that may offer shorter, safer, more effective and more convenient AIT (Table 1).

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9b MECHANISMS OF ALLERGEN IMMUNOTHERAPY

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Allergen immunotherapy (AIT) utilizes multiple mechanisms, which elicit rapid desensitization and long-term allergen-specific immune tolerance as well as the suppression of allergic inflammation in the affected tissues.

KEY MESSAGES

- Long-term clinical and immune tolerance to allergens can be induced by AIT
- AIT mechanisms include changes in the profile of allergen-specific memory T and B cell responses, the synthesis of specific antibody isotypes towards a non-inflammatory pattern, and decreased activation, tissue migration and degranulation of effector cells including mast cells, basophils and eosinophils
- The shift in the balance from allergen specific Th2 toward Treg cells is central to development of allergen tolerance
- Novel biomarkers are needed to aid the selection of the best AIT responders

IMMUNE TOLERANCE TO ALLERGENS

Long-term clinical and immune tolerance to allergens can be induced by AIT. Its mechanisms include changes in the profile of allergen-specific memory T and B cell responses, the synthesis of specific antibody isotypes towards a non-inflammatory pattern, and decreased activation, tissue migration and degranulation of effector cells including mast cells, basophils and eosinophils (Figure 1).

DESENSITIZATION OF EFFECTOR CELLS

Successful AIT is associated with the altered magnitude of mediator release from the effector cells below the "normal" threshold of systemic anaphylaxis. The shift in the balance between allergen specific Th2 and Treg cells is central to either development of allergen tolerance during AIT and the recovery from allergic disease (Figure 1). In both healthy and allergic individuals three major types of allergen-specific subsets of T cells, the Th1, Th2 and Tr1 cells, are to be found in different proportions. Studies with MHC-class II tetramers showed a switch from dominating IL-4-producing T-cells to the FOXP3-positive and IL-10-producing antigen-specific CD4+ T-cells. T cell suppression can take place both in the secondary lymphoid organs and in the affected tissues.

Allergen-specific IgE and IgG responses.

Allergen-specific B cells do not show tolerance or unresponsiveness to allergens but skew from IgE-producing to IgG4-producing cells. IL-10 regulates isotype formation towards a non-inflammatory phenotype – IgG4. IgG4 is also a blocking antibody that prevents the activation and degranulation of effector cells. The shift in isotype production cannot however, explain the therapeutic effect of SIT probably due to a very long life span of IgE-producing plasma cells in the bone marrrow.

Suppression of allergic inflammation

AIT efficiently modulates IgE-mediated activation and histamine release from mast cells and basophils due to Treg cell-dependent mechanisms. IL-10 also downregulates eosinophil function and ac-

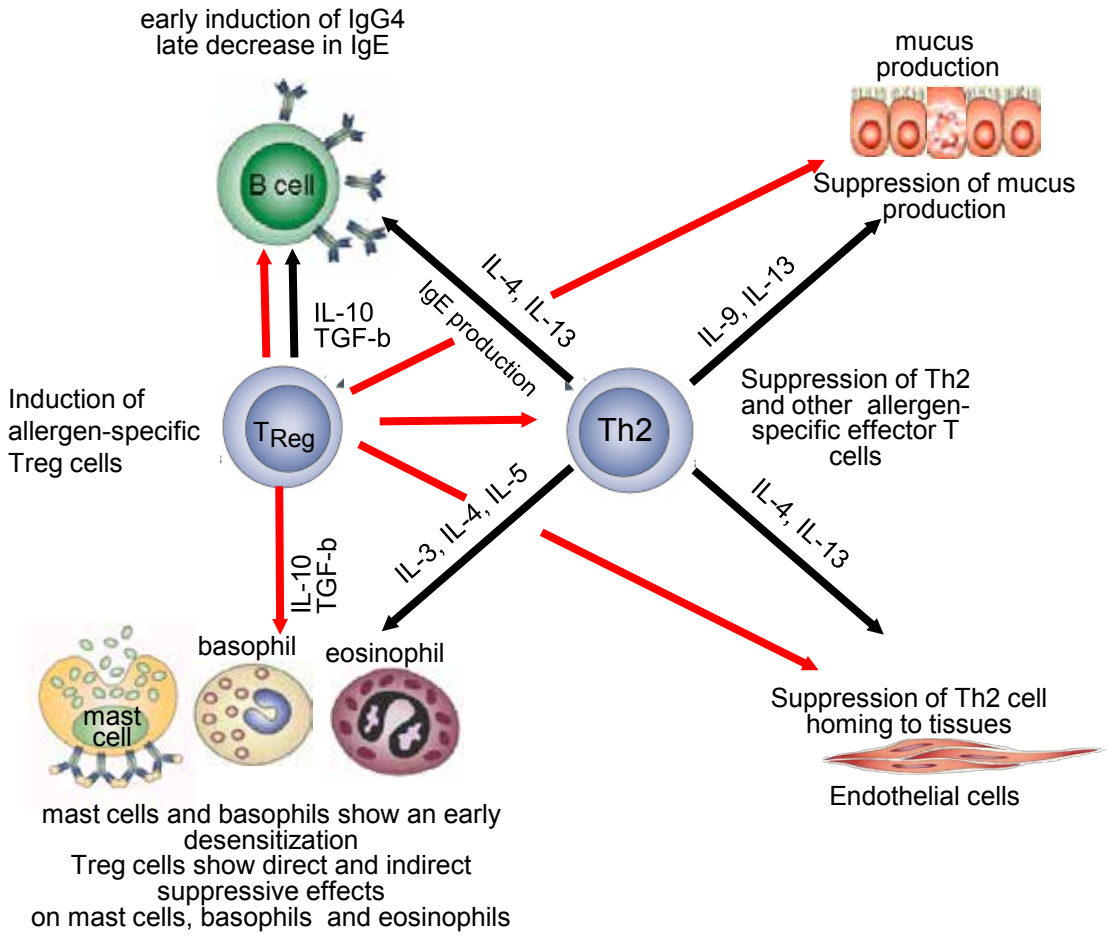

Figure 1 Mechanisms of long-term immune tolerance obtained by allergen-specific immunotherapy. After the first administration of the AIT vaccine, there is an early decrease in mast cell and basophil degranulation and a decreased tendency for systemic anaphylaxis due to early desensitization. Then, allergen-specific Treg cells are generated and there is suppression of allergen-specific Th2 cells and other effector cells. Due to immune tolerance in Th2 cells, they can no longer contribute to IgE production, endothelial cell activation and Th2 cell homing to tissues, mucus production by the epithelium, and tissue migration, priming and survival of mast cells, eosinophils and basophils. IL-10 and TGF-β directly and indirectly regulate B cells and effector cells. Other T cell subsets such as Th1, Th9, Th17 and Th22 are suppressed by Treg cells. Within the spectrum of changes in the immune system after SIT, there is a relatively early increase in the amount of IgG4 and a late decrease in IgE. A substantial decrease in the allergen-specific IgE/IgG4 ratio occurs after several months. A decrease in tissue mast cells and eosinophils and release of their mediators and decrease in late phase response is observed in the affected tissues.

tivity directly or by suppression of IL-5 production and reduces proinflammatory cytokine release from mast cells and. AIT results in decreased numbers of eosinophils and their mediators in the mucosal tissues .

FUTURE PERSPECTIVES

Novel early and late diagnostic biomarkers should be validated to provide help in the selection of the best AIT responders as wells in the optimizing of their treatment. The advances in immunology and bioengineering provide improved approaches based on both the newer vaccines as well as combination of AIT and biological treatment. The better understanding of the AIT mechanisms will also help in elaboration of efficient prevention strategies and very early intervention in pediatric subjects (Table 1).

TABLE 1

What is unknown in the mechanisms of allergen immunotherapy
• Molecular mechanisms of how Treg cells are generated in vivo
• Better adjuvants that specifically induce Treg cells
• In vivo life span of Treg cells induced by AIT
• Potential deleterious roles of Treg cells, such as immune tolerance to tumor antigens and chronic infectious agents
• Role of resident tissue cells in immune tolerance
• Molecular mechanisms of spontaneous healing, remissions and exacerbations of allergic disease
• Local tissue events during SLIT and epicutaneous AIT
• Early molecular markers and predictors to decide AIT start, stop and success
• Differences between the mechanisms of high and low dose AIT
• Mechanisms of long term maintenance of allergen tolerance

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9c SUBCUTANEOUS ALLERGEN IMMUNOTHERAPY

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KEY MESSAGES

- Subcutaneous allergen immunotherapy (SCIT) reduces the symptoms of allergic diseases and the need for medication, on top of the reduction of symptoms already obtained by pharmacotherapy
- SCIT is indicated for allergic rhinoconjunctivitis, allergic asthma and atopic dermatitis
- The beneficial effects of SCIT have been demonstrated with high-dose treatment
- After several months of SCIT the total costs of allergic respiratory disease management is lower than pharmacotherapy alone

With subcutaneous allergen immunotherapy (SCIT) allergen extract(s) are administered in a controlled, repetitive fashion, to finally create a state of tolerance, in which the patient no longer reacts to the allergen. During the build-up phase SCIT injections are administered once to twice weekly, with gradually incremental quantity of allergen (Figure 1). After reaching the projected maintenance dose the injection frequency is tapered to every 2-6 weeks, without further dose-escalation. It is crucial to reach a high level of allergen for SCIT to be effective ('high dose' SCIT). SCIT is allergen-specific, resulting in tolerance to only those allergens administered in the SCIT. A correct diagnosis of those allergens responsible for the patient's symptoms is mandatory. Administration of too many allergens simultaneously is probably less effective. As such, the prescribing physician has to be thoroughly trained in allergy and SCIT to interpret skin prick tests or serologic testing correctly and select the right allergens for SCIT.

SCIT has been shown to be effective for several allergic diseases (Figure 2). High quality scientific evidence (Cochrane meta-analysis) has shown that SCIT improves symptoms and reduces medication use in allergic rhinitis, allergic asthma, allergic conjunctivitis, atopic dermatitis and severe allergic reactions to hymenoptera venom. Its use in latex allergy is still investigational. Due to the risk of severe adverse reactions, SCIT should not be used for the treatment of food allergy, urticaria or anaphylaxis. When given at the right dose SCIT with extracts of grass, tree and weed pollen is effective, as well as with house dust mite, animal dander and hymenoptera venom. However, SCIT has till now only shown efficacy with a limited number of molds (e.g. *Alternaria* and *Cladosporium*).

When applied in the correct way and by a specialized physician SCIT is generally safe. Local and systemic adverse reactions can occur (Figure 3). Due to safety reasons injections are withheld in unstable patients and during acute illnesses. Patients with severe allergic diseases –such as severe or uncontrolled asthma- are not candidate for SCIT, nor are patients who take systemic beta-blockers.

High dose SCIT reduces the symptoms of allergic diseases and the need for medication, on top of the reduction of symptoms already provided by pharmacotherapy. SCIT is the only disease modifying treatment available today. The effects of SCIT last beyond the duration of the treatment (Figure 4). In children with allergic rhinitis

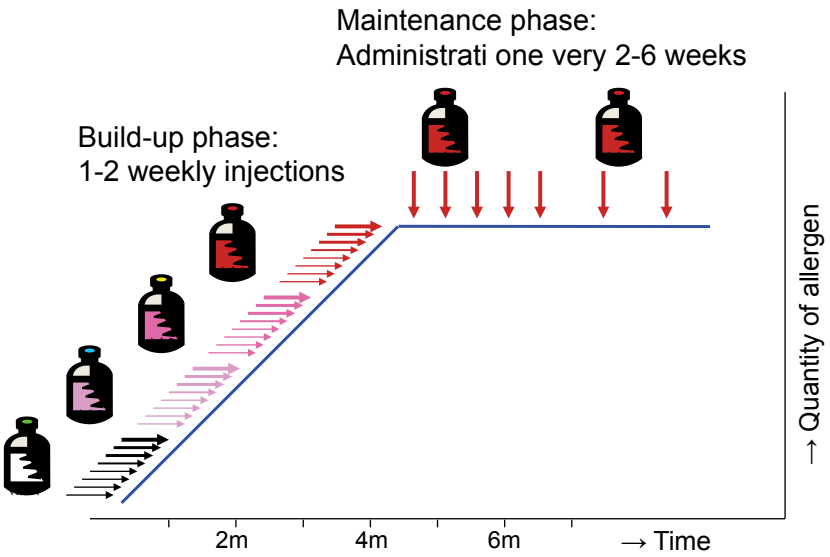

Figure 1 General dosing schedule for SCIT. On avarage the build-up phase lasts 3-6 months, during which the allergy shots are given 1-2 times/week; in the the maintenance phase injections are given every 2-6 weeks for at least 3 years.

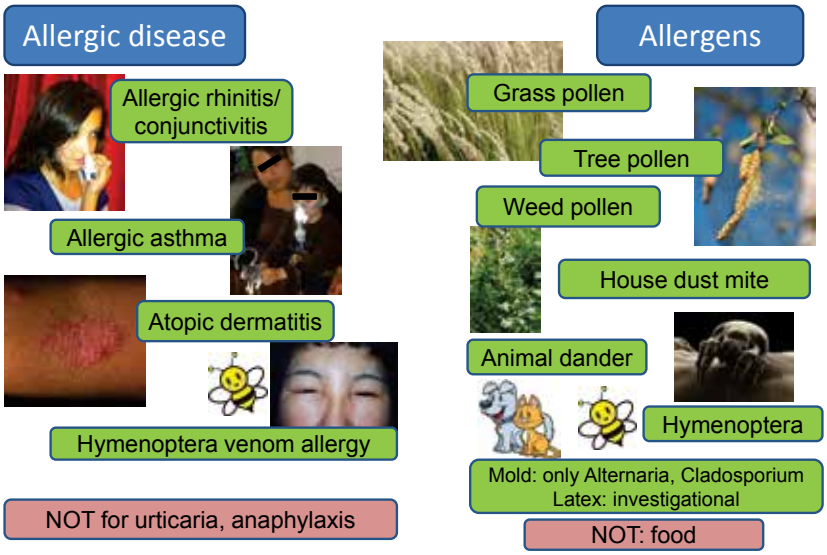

Figure 2 Indications for SCIT (diseases and allergens where SCIT proved efficacios).

a three year course of high-dose SCIT reduced the risk of developing allergic asthma even seven years after discontinuation of AIT (Figure 5).

Although AIT is costly, after several months of SCIT the total costs for the management of allergic respiratory diseases are lower compared to pharmacotherapy alone.

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Figure 3 SCIT adverse reactions. SCIT can result in local adverse reactions with wheal and flare and pruritus at the injection site. Sometimes, mild systemic reactions can be documented and very rare severe systemic reactions occur. Consequently, SCIT should be applied under surveillance in an allergist office.

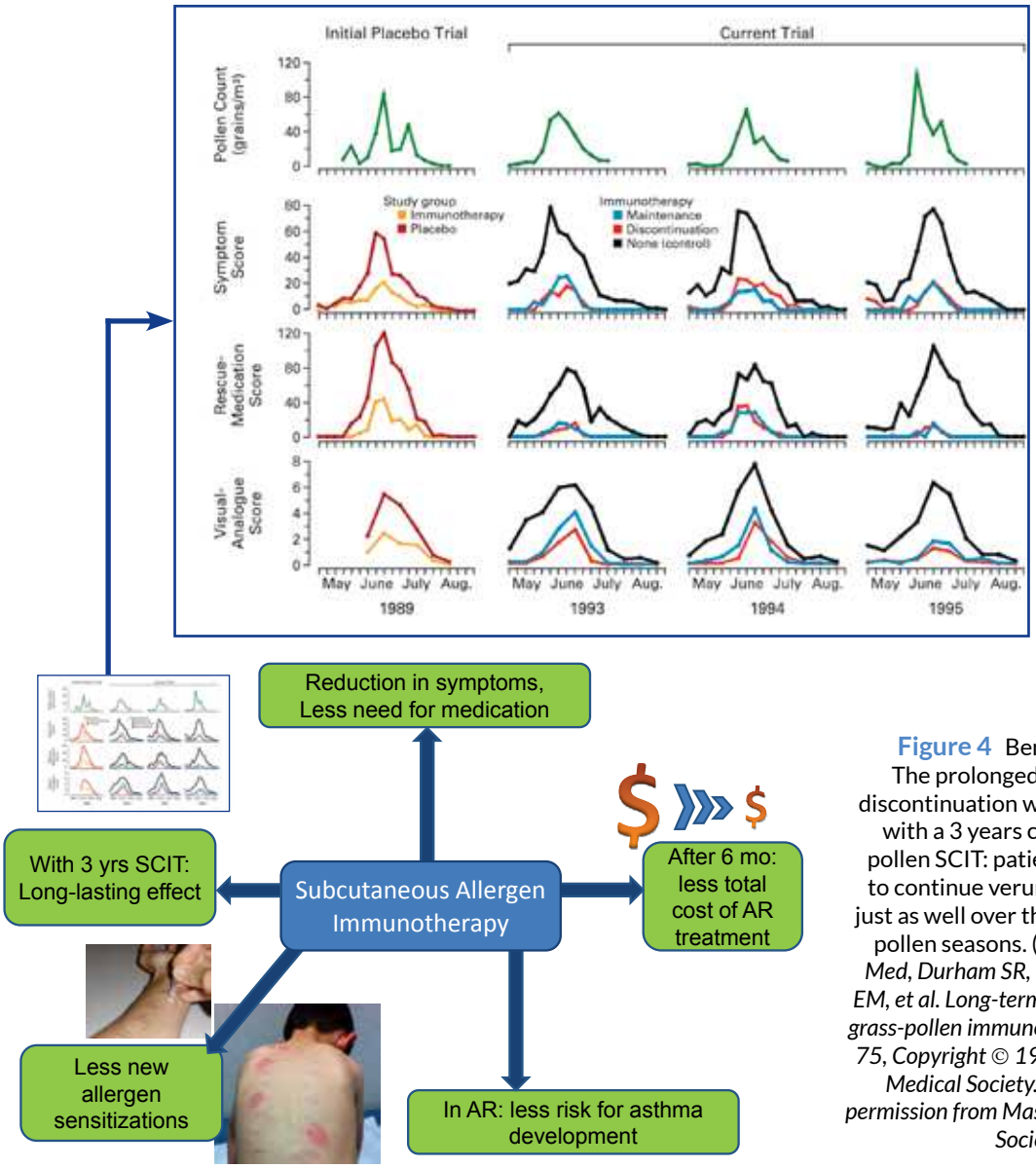

Figure 4 Benefits of SCIT. The prolonged efficacy after discontinuation was demonstrated with a 3 years course of grass-pollen SCIT: patients randomized to continue verum or placebo did just as well over the following three pollen seasons. (*From New Engl J Med, Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy, 341,468-75, Copyright © 1999 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.*)

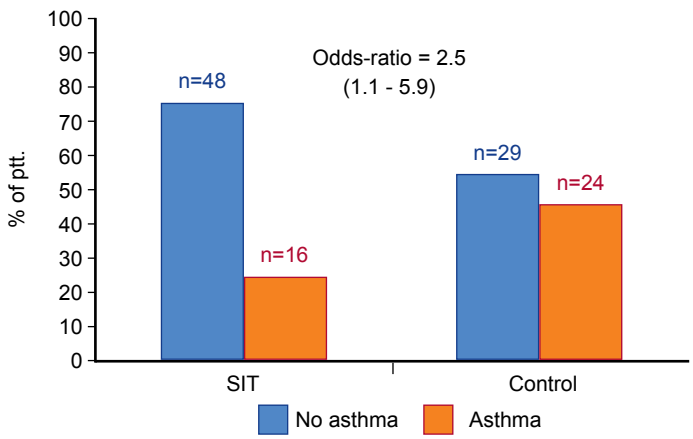

Figure 5 SCIT reduces the risk of developing asthma in children with allergic rhinitis. A three year SCIT course in children with allergic rhinitis showed a reduced risk for developing asthma 7 years after SCIT was stopped. (*Reproduced with permission from Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007;62:943-8, with permission from Willey Blackwell.*)

9d SUBLINGUAL ALLERGEN IMMUNOTHERAPY

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KEY MESSAGES

- Sublingual allergen immunotherapy (SLIT) was proposed as an alternative to subcutaneous allergen immunotherapy as a new therapeutic easy-to-take intervention with a better safety profile
- The clinical efficacy and the improved safety profile have been proven in large randomised clinical trials, both in the adult and the pediatric population
- Doses of 15 to 25 micrograms of the major allergy protein are recommended to obtain a statistically significant clinical improvement
- The long-lasting effect was proven in a randomised trial in patients with moderate-to-severe grass pollen-induced allergic rhinoconjunctivitis

In the 80's, sublingual allergen immunotherapy (SLIT) was proposed as an alternative to subcutaneous allergen immunotherapy. The main purpose was to provide the increasing allergic population a new therapeutic easy-to-take intervention with a better safety profile. Since then, the clinical efficacy and safety of SLIT have been thoroughly evaluated mainly for aeroallergens for respiratory allergy. New standardised products are currently commercially available worldwide. SLIT can be administered as drops or fast-dissolving tablets.

Efficacy. Evaluating data from randomised double-blind placebo control trials, the clinical efficacy (assessed as the reduction of symptoms scores and the need of rescue medication) of SLIT for allergic rhinitis, allergic asthma, allergic conjunctivitis, house dust mite allergy and grass allergy, has been confirmed in various meta-analyses (Table 1). Significant clinical and methodological heterogeneity was shown amongst included studies (Table 1). More recently, well-powered studies using a large number of adult and paediatric patients suffering from moderate to severe allergic rhinoconjunctivitis due to grass pollen, with or without asthma, inadequately controlled by symptomatic medications have been performed. These studies have confirmed the clinical efficacy of SLIT in reducing nasal and ocular symptoms and the use of relief symptomatic medication. Also, improvement in quality of life has been consistently found using SLIT. No difference in clinical efficacy of single-allergen grass pollen SLIT was observed between mono- and poly-sensitised subjects. Doses of 15 to 25 micrograms of the major allergy protein are recommended to obtain a statistically significant clinical improvement.

Safety. SLIT safety profile is very good. Drops and tablets are well tolerated by both children and adults. The most common adverse reactions due to SLIT are localised to the oral mucosa; 65-85% of the patients may complain of itching, lip/tongue swelling or ear pruritus. These are mild, self-limited symptoms which appear 10-15 min or a few hours after taking the SLIT preparation and last less than 14 days. Systemic reactions are rare, but may appear, especially during the up-dosing phase. Systemic symptoms could be mild urticaria, angioedema and asthma. Only 11 cases of anaphylaxis have been reported in over 2 billion doses of

TABLE 1

Comparison between SLIT studies

Disease	Author	Population	Studies (n)	Participants		Effect Size	Heterogeneity
				Active (n)	Placebo (n)	SMD (95% CI)	I^2
Symptom Scores							
Rhinitis	Wilson D 2003	Adults and children	21	484	475	-0.42 (-0.69, -0.15)	73%
Rhinitis	Penagos M 2006	Children	10	245	239	-0.56 (-1.01, -0.10)	81%
Rhinitis	Radulovic S 2011	Adults and children	49	2333	2256	-0.49 (-0.64, -0.34)	81%
Asthma	Calamita Z 2006	Adults and children	9	150	153	-0.38 (-0.79, 0.03)	64%
Asthma	Penagos M 2008	Children	9	232	209	-1.14 (-2.10, -0.18)	94%
Conjunctivitis	Calderon MA 2011	Adults and children	36	1725	1674	-0.41 (-0.53, -0.28)	59%
House Dust Mites	Compalati E 2009	Adults and children	8	194	188	-0.95 (-1.77, -0.14)	92%
Grass Allergens	Di Bona D 2010	Adults and children	19	1518	1453	-0.32 (-0.44, -0.21)	56%
Medication Scores							
Rhinitis	Wilson D 2003	Adults and children	17	405	398	-0.43 (-0.63, -0.23)	44%
Rhinitis	Penagos M 2006	Children	7	141	138	-0.76 (-1.46, -0.06)	86%
Rhinitis	Radulovic S 2011	Adults and children	38	1737	1642	-0.32 (-0.43, -0.21)	50%
Asthma	Calamita Z 2006	Adults and children	6	132	122	-0.91 (-1.94, 0.12)	92%
Asthma	Penagos M 2008	Children	7	192	174	-1.63 (-2.83, -0.44)	95%
Conjunctivitis	Calderon MA 2011	Adults and children	13	560	478	-0.10 (-0.22, 0.03)	34%
House Dust Mites	Compalati E 2009	Adults and children	4	89	86	-1.88 (-3.65, -0.12)	95%
Grass Allergens	Di Bona D 2010	Adults and children	17	1428	1358	-0.33 (-0.50, -0.16)	78%

Effect size (SMD): poor <-0.20; medium = -0.50; high >-0.80

Heterogeneity (I2)= 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity

SLIT administered worldwide. No fatalities due to SLIT have been registered.

The first SLIT dose should be taken in the presence of a doctor (observation period of 30-60 minutes). In this way, patients are reassured about the safety of SLIT, their follow-up can be organised and compliance structured. SLIT drops or tablets are recommended to be taken at home for 3 years as continuous treatment during the year or as pre- and co-seasonal treatment.

Long-term effect. The effect of disease modification of an SQ-standardised grass SLIT-tablet 2 years after 3 years of treatment has been shown in a randomised trial in patients with moderate-to-severe grass pollen-induced allergic rhinoconjunctivitis. Outcomes such as rhinoconjunctivitis symptom and medication scores, combined scores, quality of life, days with severe symptoms, immunologic end points, and safety parameters were all improved in the SLIT-tablet group compared with the placebo group.

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9e

ORAL ALLERGEN IMMUNOTHERAPY FOR FOODS

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Oral allergen immunotherapy (OIT) for foods is one of the most studied research options for the treatment of food allergy (FA) in young children. At this time, management of FA consists of strict dietary avoidance of the allergen and access to readily available epinephrine. Despite increased vigilance with food allergen avoidance, inadvertent exposure to the allergen is common and can result in potentially life-threatening reactions. There is a strong unmet need for the development of disease modifying therapies for the treatment of FA and to develop a cure for FA.

In the early 20th century, a report of a successful OIT regimen for the treatment of egg allergy was published in the Lancet. Recently, significant progress has been made in studying this strategy for the treatment of FA.

KEY MESSAGES

- There is currently no approved treatment available for food allergy and management consists of strict dietary avoidance of the allergen and access to readily available epinephrine
- Oral immunotherapy (OIT) for foods is an experimental and research modality
- Preliminary data for OIT is encouraging and has shown that OIT can be effective for raising the amount of food needed to cause an allergic reaction
- OIT for foods is not ready for everyday use in clinical practice. Data are lacking regarding long-term safety and efficacy
- Further research and large, well designed, multicenter, randomized, double-blind, placebo-controlled clinical trials are needed before OIT can be used in clinical practice

WHAT IS INVOLVED IN THE ADMINISTRATION OF OIT?

During OIT, doses of the food allergen (which are in the form of a powder) are mixed in a food vehicle (such as pudding, ice-cream etc.) and are ingested by the individual in gradual incremental doses, starting with extremely small amounts (Figure 1). This is in contrast to sublingual immunotherapy in which small drops of allergen extract are placed under the tongue, and are then swallowed or spit out.

While the exact protocol may vary, most OIT studies consist of an initial dose escalation phase that is carried out in a closely supervised setting such as a research study center, followed by buildup and maintenance phases that are typically completed at home. Individuals require close monitoring and must be evaluated at regular intervals (Figure 2).

The optimal duration for OIT for foods is unclear at this time. Standard immunotherapy for aeroaller-

Figure 1 A maintenance dose of peanut OIT (consisting of peanut flour). This is mixed in a food vehicle (such as pudding, ice-cream etc.) before ingestion by the individual.

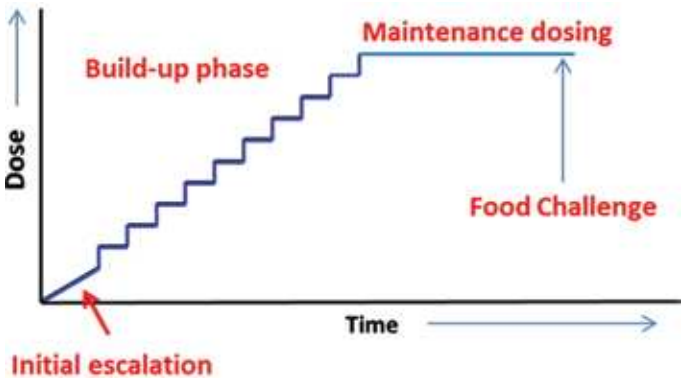

Figure 2 Oral Immunotherapy for Food Allergy. (*Reproduced with permission from Kulis M, Burks AW. Oral immunotherapy for food allergy: Clinical and preclinical studies. Advanced Drug Delivery Reviews 2013;65:774-781.*)

TABLE 1

Factors increasing the risk of an allergic reaction for individuals on OIT for food allergy
• Acute febrile illness or viral illness
• Menses
• Prolonged exertion/ after exercise
• Inadequately controlled asthma
• If doses of OIT are taken on an empty stomach

TABLE 2

Immunologic changes seen during OIT for foods
↓ food allergen specific IgE antibodies
↑ food-specific IgG4 antibodies (inferring a possible protective effect)
↓ activation of mast cells shown by decreased size of food allergen specific skin prick tests
↓ basophil activation tests
↓ cytokines associated with an allergic profile (Th2 cytokines)

TABLE 3

The differences in the concept of desensitization and tolerance in OIT studies for food allergy	
Desensitization	**Tolerance**
• Desensitization refers to a protective effect that requires daily, uninterrupted consumption of the food allergen or OIT in order to maintain protection or a desensitized state	• Tolerance implies that a food allergen could be ingested without symptoms of an allergic reaction, despite prolonged periods of avoidance and even when OIT is discontinued
• If the dosing of OIT or consumption of the food allergen is interrupted or discontinued, this protective effect can be lost.	• Even if the dosing of OIT or consumption of the food allergen is interrupted or discontinued, the protective effect should persist
• In research studies, desensitization is measured by conducting a supervised oral food challenge while the individual is taking OIT	• The optimal way to measure tolerance is unknown. In research studies, this concept is tested by interruption of OIT dosing for at least 4 weeks or longer followed by a supervised oral food challenge

gens and insect venoms is continued for a period of 3-5 years, so it may be reasonable to estimate that OIT for foods would require a similar time commitment.

Adverse reactions to OIT are common and can range from mild allergic symptoms to severe reactions that require treatment with epinephrine (Table 1).

OIT for foods is not ready for clinical practice and remains an investigational approach at this time. Preliminary data is encouraging and has shown that OIT can be effective for peanut, milk and egg allergy and clinical improvements have been associated with favorable immunologic changes (Table 2). Many questions remain unanswered, such as tolerance versus desensitization mechanisms involved in OIT (Table 3), and long term data is lacking regarding safety and efficacy. Large, well designed, randomized, double-blind, placebo-controlled clinical trials are needed before OIT is ready for use in clinical practice.

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9f RECOMBINANT ALLERGENS FOR ALLERGEN IMMUNOTHERAPY

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KEY MESSAGES

- Allergen-specific immunotherapy is the only allergen-specific and disease-modifying treatment for allergy
- Almost all clinically relevant allergen molecules are available in recombinant form and are used for diagnosis and immunotherapy
- Several clinical studies have demonstrated efficacy of recombinant allergen-based immunotherapy
- On the basis of recombinant allergens it will be possible to make allergy vaccines more safe, convenient and effective

Allergy is a major health problem for more than 25% of the population. Allergic patients produce IgE antibodies against a variety of allergens, which upon inhalation, ingestions, skin contact and systemic administration cause severe inflammatory reactions. Allergen-specific immunotherapy (AIT) is the only allergen-specific and disease-modifying treatment with long-lasting effects . It is based on the administration of the disease-causing allergens in the form of vaccines. AIT with a grass pollen allergen extract was performed already in 1911 for the first time and since then is still based on crude allergen extracts. However, the use of such crude allergen extracts is a major bottle neck for the development of safe and effective allergy vaccines with convenient administration schedules because the composition of allergen extracts shows variations, cannot be controlled by the manufacturer and the administration of natural allergens can cause severe side effects. Accordingly, only too few patients can benefit from SIT and the compliance of SIT-treated patients is low. The majority of allergic patients is therefore treated only with symptomatic anti-inflammatory medications.

MOLECULAR CHARACTERIZATION OF ALLERGENS: RECOMBINANT ALLERGENS

The possibility of isolating the genes coding for allergens by molecular cloning has allowed to characterize the structures of most of the clinically relevant allergens and to produce them as recombinant allergen molecules in unlimited amounts and in consistent quality (Figure 1). Furthermore, several technologies based on genetic engineering of the recombinant allergens have been developed to reduce the allergenic activity of allergy vaccines and thus to increase the safety of AIT. In addition, genetic engineering delivers recombinant allergen derivatives with increases immunogenicity thus inducing protective immunity with fewer administrations.

The first immunotherapy trial based on recombinant allergens was indeed performed with genetically modified recombinant allergen derivatives of the major birch pollen allergen, Bet v 1 and since then several successful clinical trials have been performed based on recombinant allergen molecules.

Companion diagnostic tools based on micro-arrayed recombinant allergen molecules have been developed, which allow to determine the patients reactivity profile and thus to select the optimal allergy vaccines for treatment. Furthermore, the effects of vaccination can be assessed with the micro-arrays by simple blood testing.

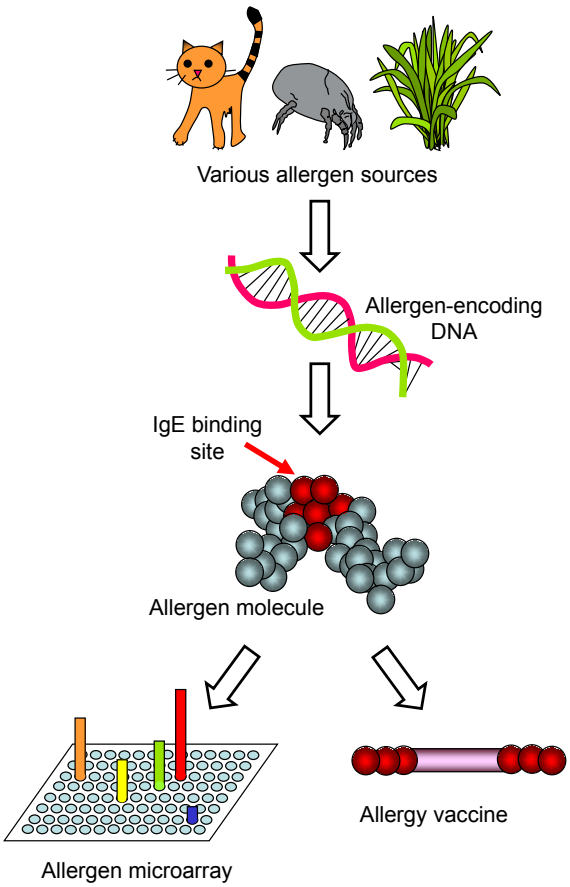

Figure 1 From allergen genes to allergy vaccines. Based on the genes coding for allergens, recombinant allergen molecules and hypoallergenic derivatives can be made for allergen-specific immunotherapy.

ADVANTAGES OF RECOMBINANT ALLERGEN-BASED ALLERGY VACCINES

Recombinant allergen-based vaccines offer many important advantages and thus will revolutionize AIT. First, they contain defined amounts of the allergen components, which can be manufactured in consistent quality with defined molecular and immunological characteristics. The composition of the vaccine can be tailored according to patient's sensitizations. Together with recombinant allergen-based diagnostic tests as companion diagnostics one can expect more and more personalized and stratified treatments becoming available which suit the individual allergic patients best. Importantly, the allergenic activity of the vaccines can be strongly reduced so that the risk of side effects can be minimized. This allows avoiding inconvenient up-dosing schedules and treatments based on numerous injections or daily administrations. Instead it will be possible to treat patients with an optimal dose from the beginning with only few injections.

Recombinant allergen-based vaccines have been developed and successfully evaluated for several respiratory allergen sources and recently also for severe forms of food allergy (http://www.allergome.org:8080/fast/index.jsp).

Scientific projects and trials are on their way to explore the potential usefulness of recombinant allergen-based vaccines for the prophylaxis of allergy with a view towards the prevention of allergic sensitization .

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9g PEPTIDE IMMUNOTHERAPY FOR ALLERGIC DISEASE

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KEY MESSAGES

- Pharmacotherapy for allergic diseases treats symptoms only, must be taken continuously to maintain symptom relief and does not modify the underlying disease process
- Allergen immunotherapy (subcutaneous and sublingual) for allergic rhinitis, using whole allergen preparations, is clinically efficacious and provides symptom relief that exceeds the duration of treatment
- Despite favourable efficacy, immunotherapy compliance is poor due to allergic side effects associated with the treatment and resulting protracted treatment course
- Peptide immunotherapy reduces IgE-mediated adverse events, thereby improving safety. A short course of 4 intradermal injections provided symptom relief for at least two years

Allergen immunotherapy (AIT) is clinically effective and, unlike pharmacotherapy, is disease modifying. The duration of clinical efficacy exceeds the period of treatment. AIT has been shown to prevent progression of allergic rhinitis towards asthma and to reduce the risk of developing new allergic sensitizations. However, AIT is associated with frequent adverse events (mainly local, but also potentially systemic) related to the fact that patients are administered the allergen to which they are sensitized. Both subcutaneous and sublingual immunotherapy are associated with poor compliance.

The allergenicity of whole allergen used in AIT is determined by the presence of B cell epitopes, which cross link allergen-specific IgE on effector cells, such as mast cells and basophils.

The mechanisms of action of AIT are incompletely understood, but are known to involve modulation of both the T cell (e.g. induction of regulatory T cells) and B cell response (e.g. induction of allergen-specific IgG). It remains unclear, which of these effects, or indeed other currently unknown mechanisms, are primarily responsible for efficacy.

Based on the hypothesis that allergen-specific T cells coordinate allergic inflammation and that B cell epitopes on whole allergens are primarily responsible for adverse events, a peptide immunotherapy approach has been developed using short linear peptide sequences constituting the dominant T cell epitopes of several major allergens (e.g. cat, house dust mite, grass).

In double-blind, placebo-controlled, clinical trials conducted under controlled allergen exposure conditions in environmental exposure chambers/units, subjects were exposed to allergen, before and after treatment over a three month period (four or eight intradermal injections at 4 weeks intervals). Clinical efficacy was assessed as change from baseline in Total Rhinoconjunctivitis Symptom Score (TRSS) at different time points after the initiation of treatment. Clinical efficacy was demonstrated with peptide immunotherapies for cat allergy (Figures 1 and 2), house dust mite allergy and grass pollen allergy. Treatment effects were greater in severe symptomatic subjects. Adverse events profiles were similar to placebo in all cases.

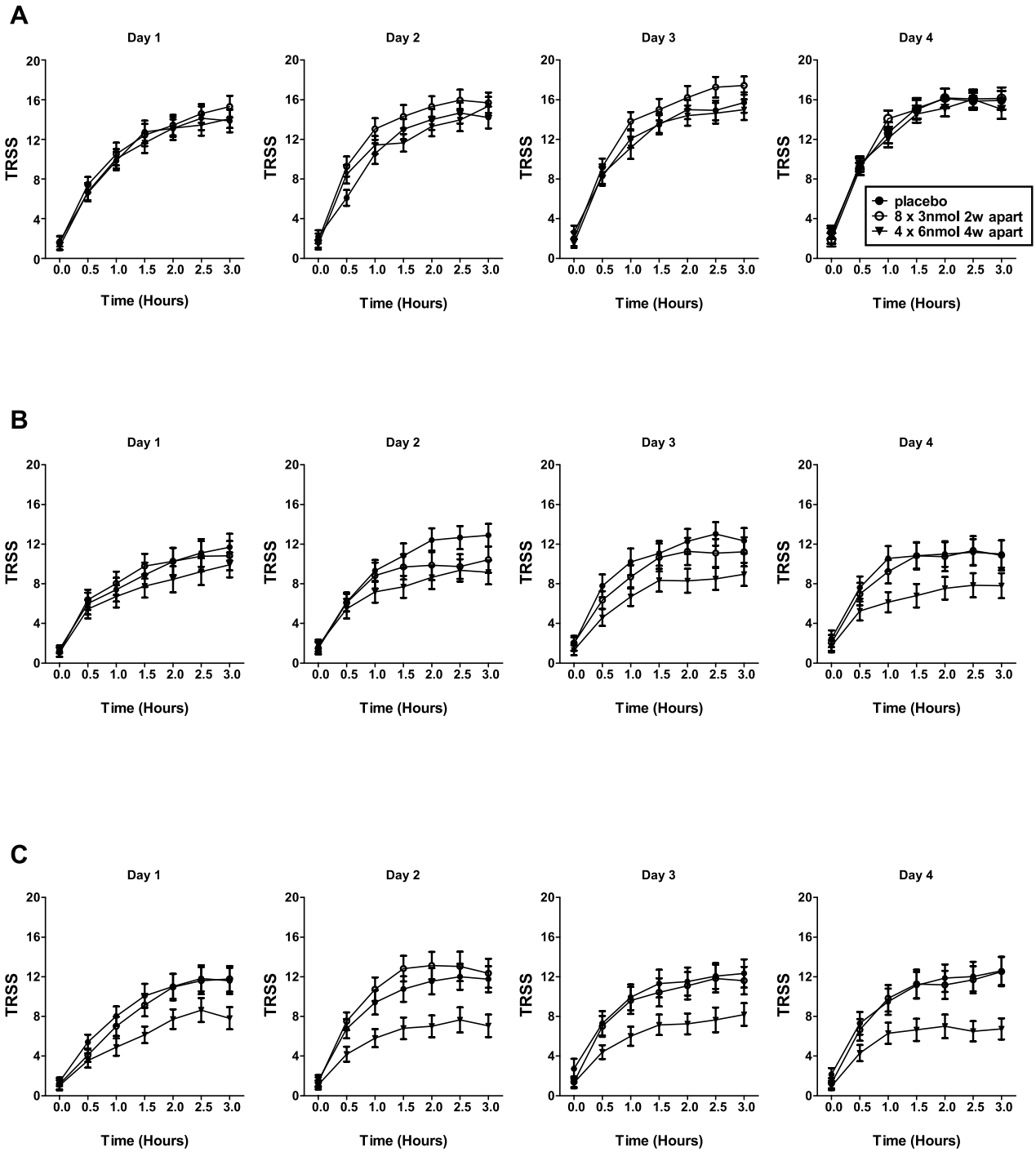

Figure 1 TRSSs (means 6 SEMs) at each 30-minute time point (3 hours per day) in the chamber over 4 consecutive days: score at baseline (A), score at 18 to 22 weeks after the start of treatment (B), and score at challenge 50 to 54 weeks after the start of treatment (C). (*Reprinted from J Allergy Clin Immunol, 131/1, Patel D,Couroux P, Hickey P, et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study, 103-109, Copyright 2013, with permission from Elsevier.*)

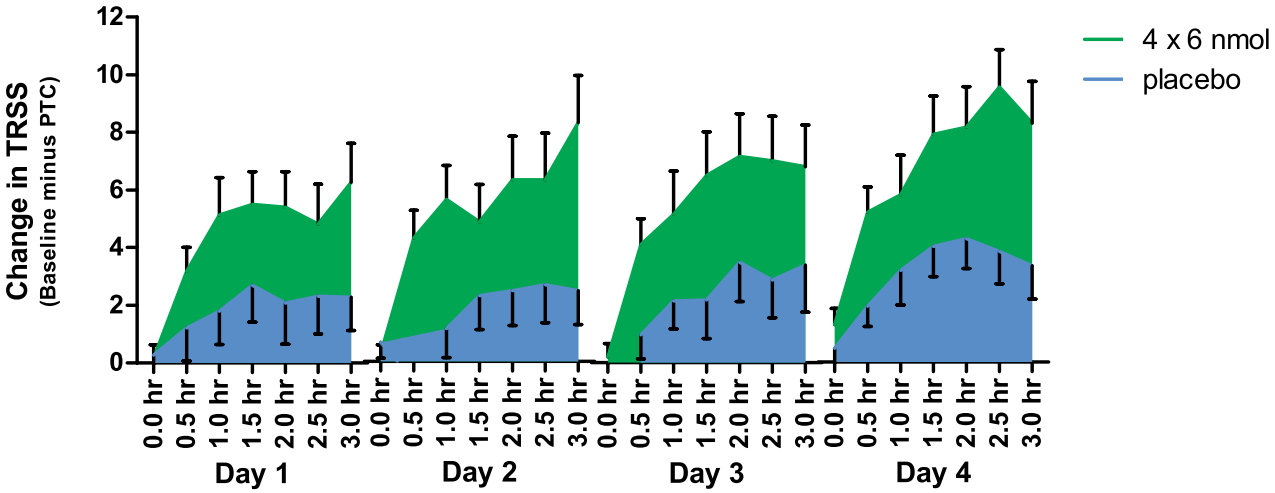

Figure 2 Difference in TRSSs (means 6 SEMs) at each 30-minute time point (3 hours per day) in the chamber over 4 consecutive days: score at baseline challenge minus score at PTC 50 to 54 weeks after start of treatment. (*Reprinted from J Allergy Clin Immunol, 131/1, Patel D,Couroux P, Hickey P, et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study, 103-109, Copyright 2013, with permission from Elsevier.*)

Thus, peptide immunotherapy may provide a solution to the poor compliance, high rates of adverse events and protracted course of treatment associated with traditional forms of allergen immunotherapy (subcutaneous or sublingual) performed with intact allergens. The persistence of clinical efficacy for months to years after a short course of treatment suggests that the goal of safe, long-term disease modification in a manner acceptable to both patients and clinicians can be achieved.

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9h NEW ROUTES FOR ALLERGEN IMMUNOTHERAPY

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KEY MESSAGES

- Current allergen immunotherapy requires numerous allergen administrations and may cause allergic adverse events
- Intralymphatic allergen delivery (ILIT) is safe and strongly enhances efficacy
- Epicutaneous allergen delivery (EPIT) is convenient and ameliorates symptoms after six patch applications
- Both, ILIT and EPIT require further clinical development with respect to dose, number and frequency of applications, and adjuvants

Allergen-specific immunotherapy (AIT) is the only treatment modality with long lasting effects that can stop progression of disease. However, due to the currently long treatment duration and potential adverse events, only a few percent of allergic patients chose to undergo AIT and adherence is very low.

In conventional subcutaneous AIT (SCIT) the allergen is injected subcutaneously (Figure 1). Most of the injected dose remains at the site of injection and causes local reactions via mast cells degranulation. Leakage of allergen to the vasculature or inadvertent intravascular injection may also cause systemic allergic reactions. Only a small fraction (<1%) of the injected allergen dose drains to the local lymph node where dendritic cells induce the T- and B-cell responses necessary for the immunotherapeutic effect.

One possibility to enhance AIT potency and to decrease adverse events is by delivering the allergen directly into lymph nodes, where the density of antigen-presenting dendritic cells and responding T- and B-cells is maximal, so called intralymphatic immunotherapy (ILIT). Another route, the epicutaneous allergen immunotherapy (EPIT), relies on the epidermis properties with a high density of antigen presenting Langerhans cells, but no mast cells and no vasculature, which should reduce local and systemic side effects.

ILIT: Direct intra lymph node injection delivers more allergen to dendritic cells, T- and B-cells. Simultaneously, local reactions should be reduced, as lymph nodes contain only few mast cells.

In fact, in the first randomized controlled trial, as little as three low dose injections of grass pollen extract into subcutaneous lymph nodes of the inguinal area proved readily feasible and painless. ILIT was found safer and showed efficacy similar to a three year perennial SCIT regimen. These first findings have been reproduced by another group in a double-blinded placebo controlled fashion. In another double-blinded placebo-controlled trial three low dose intralymphatic injections with a modified recombinant cat dander allergen (MAT-Fel d 1) were safe and induced a robust regulatory T cell responses correlating with IgG4 responses, as well as nasal tolerance to cat dander (Figure 2).

EPIT: Three double-blinded placebo controlled clinical trials were performed, where grass pollen extract was administered by application of a patch to the skin of the upper arm (Figure 3). The area of the patch application was prepared by adhesive tape stripping. All three trials found significant symptom amelioration over placebo. The total administered allergen dose was correlated with the clinical response. The application

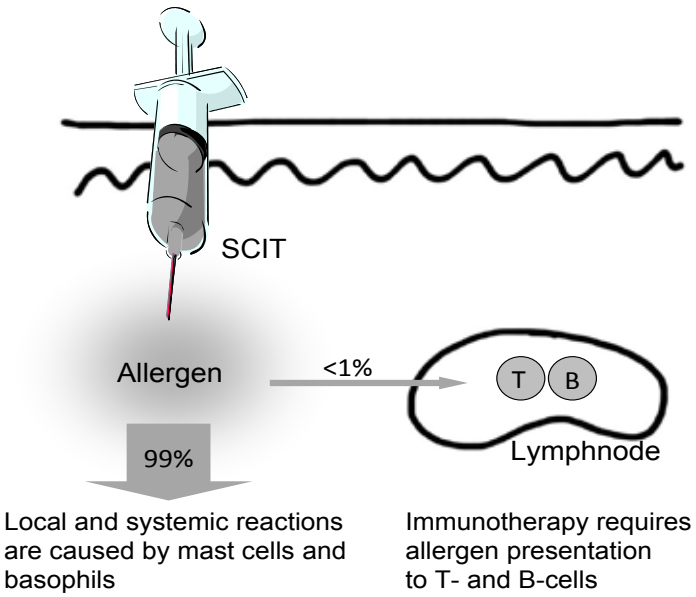

Figure 1 Conventional SCIT.

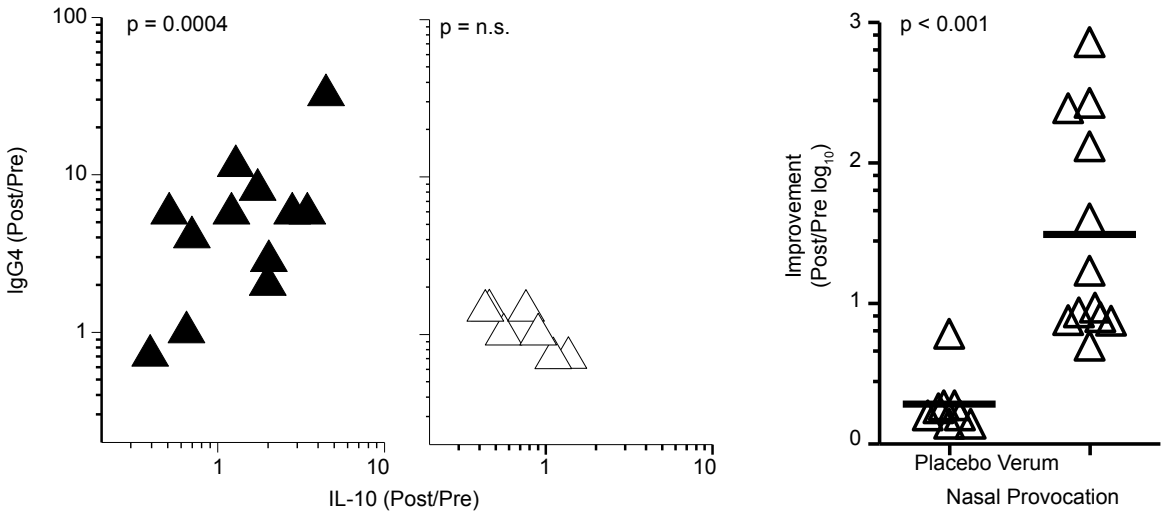

Figure 2 Intralymphatic administration of a modified recombinant cat dander allergen (MAT-Fel d 1) induced a robust regulatory T cell responses correlating with IgG4 responses (left), as well as nasal tolerance to cat dander (right). (*Reprinted from J Allergy Clin Immunol, 129/5, Senti G, Crameri R, Kuster D, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections, 1290-1296, Copyright 2012, with permission from Elsevier.*)

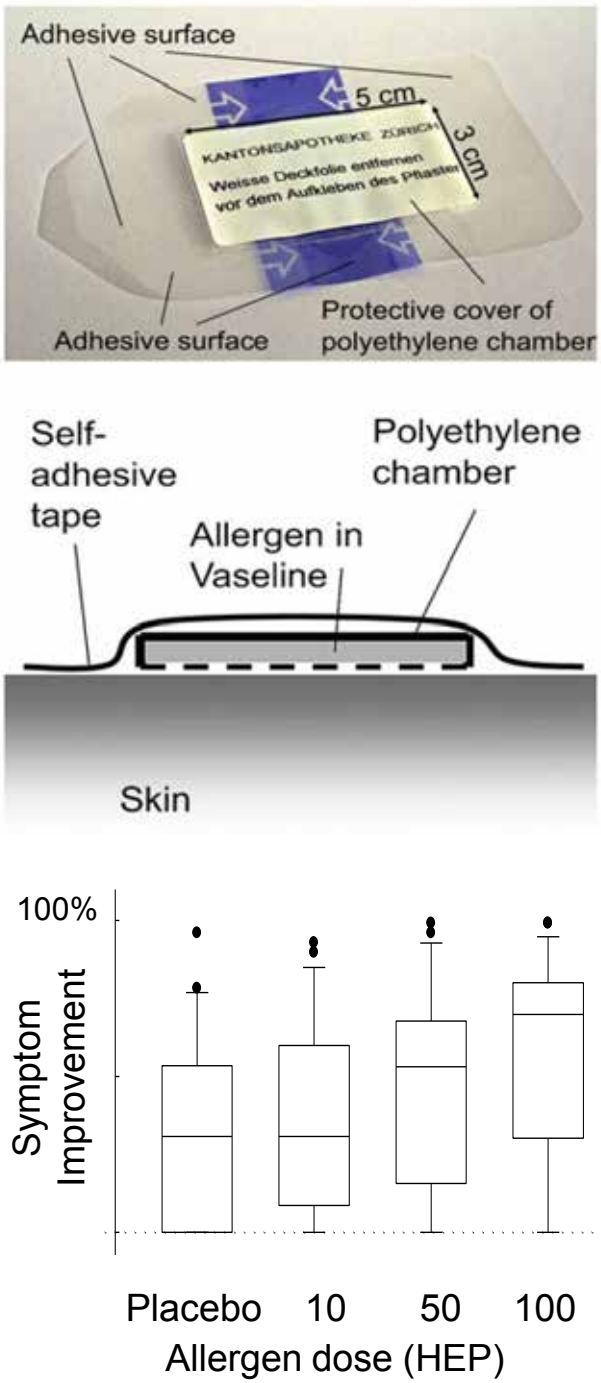

Figure 3 Epicutaneous administration via adhesive allergen strips (upper panel). The total administered allergen dose was correlated with the clinical response (lower panel). (*Reprinted from J Allergy Clin Immunol, 129/1, Senti G, von Moos S, Tay F, et al. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: A double-blind, placebo-controlled dose escalation study, 128-35, Copyright 2012, with permission from Elsevier.*)

of 6 high dose patches for 8 hours, i.e. overnight, induced symptom amelioration of 70% vs. 25% in the placebo group. When preparing the skin by adhesive tape stripping, patch application was safe. The most frequently reported adverse event was itching and mild eczema under the patch.

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9i

MEASURING CLINICAL OUTCOMES IN ALLERGEN IMMUNOTHERAPY

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KEY MESSAGES

- An EAACI Task Force recently reported measures to standardise recording of efficacy of allergen immunotherapy trials. A simple combined symptom and medication score (CSMS) is recommended as primary endpoint
- The environmental exposure chamber is recognised as a potential alternative for phase 2b trials
- Provocation testing remains important for proof of concept studies and for dose-finding
- The recent availability of recommendations for standardised reporting of side effects is a further recent advance
- Rather than reliance on a single primary endpoint, the totality of evidence should be assessed in evaluating immunotherapy

Allergen immunotherapy (AIT) is indicated in patients with moderate-severe IgE-mediated allergic rhinoconjunctivitis with/without mild asthma who fail to respond to anti-symptomatic drugs and/or experience unacceptable drug-related side-effects. Recent advances have included the availability of effective vaccines with an acceptable tolerability and safety profile.

Several documents have informed the standardised performance and reporting of clinical trials of AIT. These include guidelines for reporting AIT-related systemic adverse events and the documentation of local side effects during sublingual immunotherapy, thereby providing the opportunity for harmonisation of reporting of allergen vaccine-related side effects internationally.

An unmet need has been the standardisation of clinical and surrogate endpoints for reporting the efficacy of AIT - the objective of a recent Task Force of the European Academy of Allergy and Clinical Immunology. The documentation of symptoms during natural allergen exposure has been the gold standard with recording of 'rescue' medication as a key secondary endpoint. A recent World Allergy Organisation (WAO) position paper suggested that these two clinical outcomes are critically related and could be combined. The major recommendation is the use of a combined rhinoconjunctivitis symptom and medication score (CSMS) as the key primary outcome in AIT trials. The symptom score is recorded on a scale of 0-3 for 6 symptoms, 4 for rhinitis (itching, sneezing, runny nose and nasal blockage) and 2 for conjunctival symptoms (itchy/red eyes and eye swelling). This provides a maximum total score of 0-18/6 ie range 0-3 maximum for symptoms. There is a caveat in that for mite-induced perennial symptoms the total nasal symptom score (ie 4 symptoms, total 0-12/4, still giving 0-3 maximum) may be a reasonable alternative, as the consensus panel considered eye symptoms as less common/bothersome in mite-induced disease. The rescue medication score is recorded on a comparable 0-3 scale according to the 'as needed' daily intake of oral and/or topical antihistamine (score 1), intranasal steroid (score 2, with or without antihistamines) and oral prednisolone (maximal score 3, with/without nasal steroid and/or antihistamine). This approach provides a scale of 0-6 for the CSMS. The score is in line with the European

TABLE 1

World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of 1 organ system present* **Cutaneous** Generalized pruritus, urticaria, flushing, or sensation of heat or warmth **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis - (eg, sneezing, rhinorrhea, nasal pruritus and/ or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to originate in the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	***Symptom(s)/sign(s) of more than 1 organ system present*** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea **or** **Other** Uterine cramps	**Lower respiratory** Asthma (eg, 40% PEF or FEV1 drop NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula, or tongue edema with or without stridor	**Lower or upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death

Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4.

Note: Children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis; eg, becoming very quiet or irritable and cranky. Scoring includes a suffix that denotes if and when epinephrine is or is not administered in relationship to onset of symptom(s)/sign(s) of the SR:a, ::: 5 minutes; b, >5 minutes- to :::10 minutes; c: >10 to :::20 minutes; d:>20 minutes; z, epinephrine not administered.

*The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection*** and a suffix reflecting if and when epinephrine was or was not administered, eg, Grade 2a; rhinitis:10 minutes.*

**Each grade is based on organ system involved and severity. Organ systems are defined as cutaneous, conjunctival, upper respiratory, lower respiratory, gastrointestinal, cardiovascular, and other. A reaction from a single organ system such as cutaneous, conjunctival, or upper respiratory, but not asthma, gastrointestinal, or cardiovascular is classified as a grade 1. Symptom(s)/sign(s) from more than one organ system or asthma, gastrointestinal, or cardiovascular are classified as grades 2 or 3. Respiratory failure or hypotension with or without loss of consciousness define grade 4 and death grade 5. The grade is determined by the physician's clinical judgment.†This constellation of symptoms may rapidly progress to a more severe reaction. ***Symptoms occurring within the first minutes after the injection may be a sign of severe anaphylaxis. Mild symptoms may progress rapidly to severe anaphylaxis and death. §If signs or symptoms are not included in the table or the differentiation between a SR and vasovagal (vasodepressor) reaction, which may occur with any medical intervention, is difficult, please include comment, as appropriate.*

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TABLE 2

Grading system for sublingual immunotherapy local adverse events

Symptom/sign	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Unknown severity
Pruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema	[d] Not troublesome AND [d] No symptomatic treatment required AND [d] No discontinuation of SLIT because of local side effects	[d] Troublesome OR [d] Requires symptomatic treatment AND [d] No discontinuation of SLIT because of local side effects	[d] Grade 2 AND [d] SLIT discontinued because of local side effects	Treatment is discontinued, but there is no subjective, objective, or both description of severity from the patient/physician

Each local AE can be early (<30 minutes) or delayed

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Medicine Agency and WAO recommendations and has the advantage of simplicity. None-the-less the CSMS will require testing and validation in comparison with alternative methods in clinical trials.

Allergen provocation testing is of the value for proof of concept studies and for allergen dose-finding for subsequent phase 2b-phase 3 trials.

The use of a daily seasonal symptom and medication score is critically dependent on the pollen count, with low counts resulting in a marked reduction in power to detect treatment differences. In this context the Environmental exposure chamber was considered a potential alternative for phase 2b trials and as an adjunct to phase 3 field studies, with the caveat that this method requires standardisation within and between centres before use in multi-centre studies.

Finally it was considered that sole reliance on a single primary endpoint was undesirable and that the totality of clinical and surrogate endpoints should be taken into account when evaluating the efficacy of AIT.

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TABLE 3

Combined symptom and medication score (CSMS)		
a) Symptom score		
Nasal symptoms	(Score 0–3)	0 = no symptoms 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated) 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable) 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)
	Itchy nose	0–3
	Sneezing	0–3
	Runny nose	0–3
	Blocked nose	0–3
Conjunctival symptoms	Itchy/red eyes	0–3
	Watery eyes	0–3
(Total) daily symptom score (dSS)*		0–3 (max score is 3, i.e. 18 points/divided by 6 symptoms)
b) Medication score		
	Oral and/or topical (eyes or nose) nonsedative H1 antihistamines (H1A)	1
	Intranasal corticosteroids (INS) with/without H1A	2
	Oral corticosteroids with/without INS, with/without H1A	3
(Total) daily medication score (dMS)		0–3 (max score is 3)
c) Combined symptom and medication score		
CSMS	**dSS (0–3) + dMS (0–3)**	**0–6**

**Max score 18/6 (i.e. 4 nasal symptoms, max score 12 and 2 conjunctival symptoms, max score 6) is optimal for studies of seasonal pollino- sis. This could possibly be modified for studies of perennial allergies (e.g. in mite-allergic patients), for example max score 12/4 (i.e. 4 nasal symptoms with omission of eye symptoms). By assigning 0–3 for all individual symptoms and dividing by total number of symptoms, the symptom range 0–3 and maximum symptom score 3 would remain the same.*

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10 IMPLEMENTING A HEALTHY LIFE STYLE

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Lifestyle factors (figure 1) are discussed in the lay press as well as in scientific publications in the context of the development of many diseases, and allergies are no exception to this. While many associations have been reported, the somewhat vague term of "lifestyle" makes it difficult to disentangle the effects of different exposures summarized under this name, and adjustment for potential confounding factors is always a concern. Here, we highlight some recent advances regarding lifestyle factors such as nutrition, physical exercise/obesity, and psycho-social factors, and give hints on possibly underlying mechanisms. Additional lifestyle-factors that are not discussed here may also be of importance.

It has been proposed that lifestyle factors might influence inflammation. Diet, physical exercise, behavioral changes might influence the "steady-state level" of inflammation. This may, together with genetic susceptibility, affect different systems, including the immune response and thereby predispose to allergies. A critical window of time might be early life, although later impact on allergies and asthma cannot be excluded.

KEY MESSAGES

- Lifestyle factors are associated with the development of allergic diseases
- Studies are hampered by the difficulty to precisely define a given "lifestyle factor" for potential link to causality and by confounding factors
- Examples for lifestyle factors proposed to play important roles in the development or presentation of allergies include nutrition, physical exercise/obesity, psychological factors such as stress, and smoking
- Lifestyle factors may be operative already prenatally
- Lifestyle factors are potentially modifiable and represent prime targets for preventive interventions at the population level
- Further studies, especially interventional trials, should be given high priority

NUTRITION, PHYSICAL EXERCISE, OBESITY

Food as an essential pillar of life stands in the limelight of most, if not all, human societies, at least once starving is not a problem anymore. It is held responsible for health and disease very often, by popular belief, as well as in some cases, by scientific evidence. In the context of allergies, food components can act as triggers of allergic reactions. Additionally, the role of nutrition in the development of allergies has received much attention. For a long time, avoiding potentially allergenic food during early infancy,e.g. by delaying solid food introduction, was the accepted state of the art. More recent data, however, have challenged this approach; studies show that food diversity in the first year of life or the consumption of specific foods such as fish, goes along with decreased rates of allergic diseases. Accordingly, new recommendations do not advice parents anymore to avoid specific food for their babies in the absence of clinically manifest allergy, i.e. only for prevention.

Closely associated with nutrition on one hand and physical exercise

Figure 1 Lifestyle factors influence allergy risk.

on the other hand is obesity. Obesity was associated especially with asthma. New studies suggest that the role of obesity may already be operative prenatally. For example, maternal BMI during pregnancy was associated with the child's increased risk for asthma, but the confounding effect of the child's own overweight in mediating such effects cannot be excluded. The fact that parents impose physical restrictions on their asthmatic children to avoid asthma symptoms may result in a vicious circle further aggravating the children's situation. Management approaches including dietary interventions for weight loss and routine exercise are safe in asthmatic patients, and improve important asthma outcomes, including quality of life. Asthma care providers should learn to facilitate weight loss for their obese patients. Pharmacologic or surgical interventions for weight loss in extremely obese asthma may be considered.

SMOKING

Many patients and parents of patients spare no effort to implement actions in order to alleviate their allergies, even in the complete absence of any supporting evidence for their action. In remarkable contrast to this activism, sometimes an obvious thing to change in their lifestyle that is neglected is smoking. It cannot be stressed enough that one of the most, if not the most important potentially modifiable risk factor at least for asthma and allergic diseasesis smoking.

PSYCHOSOCIAL FACTORS

The psychosocial environment is of undisputed importance in the manifestation of allergic diseases. It is interesting to note that in German the term "Neurodermitis" is often used for atopic dermatitis, implicating a neurological/psychological component of this disease. Indeed, stress and anxiety influences e.g. skin test results. New data suggesting an association between perceived neighborhood safety and asthma or between fetal exposure to maternal stressful events and the risk of asthma and atopic diseases in childhood are intriguing, even if one takes into account the methodological difficulties, such studies have to surmount for adjusting for relevant confounders. Interventions might be suggested from studies showing the importance of psychological stress factors, although one has to admit that this might be more easily achieved on an individual rather than on a population level.

LIFESTYLE FACTORS MAY BE OPERATIVE ALREADY PRENATALLY

In addition to maternal smoking, obesity or stress during pregnancy other exposures may be relevant already prenatally. One example for this is the observation that exposure of the mother to animals goes along with a reduced risk for atopic dermatitis during the first years of life.

SUMMARY

Many studies suggest an important role for lifestyle factors. The next steps should aim at defining

even more precisely protective and harmful exposures and at investigating potential underlying mechanisms. Targeted interventional studies are needed, to realize the potential of modifying lifestyle factors for promoting health also with regard to allergies and asthma. Comprehensive interventions targeting multiple lifestyle factors are also warranted.

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11 PSYCHOLOGICAL SUPPORT IN THE MANAGEMENT OF ALLERGIC PATIENTS

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KEY MESSAGES

- Having an allergic condition can be associated with significant psychological burden for the patient and their families
- Adopting a bio-psychosocial approach when consulting with a patient with allergy ensures that the wider consequences of their allergies are addressed and not just their physical symptoms
- Psychological interventions may be helpful in the management of patients with allergic diseases and their families, but there is currently limited evidence of their effectiveness
- Clinicians need to be alert to the possibility of psychological co-morbidities, which means being attentive to changes in their patient's emotional wellbeing and be willing to work with relatives, schools or workplaces to generate a safe and supportive environment

There is increasing awareness and evidence of the psychological and social impacts of allergy on patients and their families. Psychological factors may also be an aggravating factor for allergic conditions. Stress has been recognised as a trigger for asthma and eczema, and conversely post-traumatic stress disorder may follow near fatal episodes of asthma or anaphylaxis. Under performance and lack of attentiveness may arise from the allergic symptoms themselves, from disease complications, or from allergy treatments. In children, underperformance in the classroom may have a critical impact on their educational attainment and socialisation. Food allergic children may be bullied, teased or harassed, because of the need to avoid certain foods and to carry medication with them at all times. The same applies for the need to carry rescue inhalers for asthma.

Allergic diseases rarely impact solely on the affected individual, but their effects ripple out to parents, dependents, friends and peers. Examples include eczematous itching disturbing the sleep patterns of both parents and child, or the snoring and sneezing of a rhinitic adult interrupting their partner's rest. Food avoidance within a family appears to have exceptionally far reaching impact; it may distort everyone's dietary intake, reduce family cohesion, inhibit family activities and make mealtimes particularly stressful.

So clinicians need to be constantly aware of the possible psychological effects of allergic illness and its management on both the patient and their family. Patients with an allergic disease require not just an in-depth assessment of their physical problems, appropriate medication and advice, but also consideration of and support for the psycho-social aspects of their condition (Figure 1).

There are a range of interventions used in clinical practice to help reduce patients' fears, concerns and stress and to improve their coping mechanisms. These include educational interventions and various psychological interventions, such as behavioural therapies, cognitive therapies, relaxation techniques and counselling (Table 1). Educational and psychological approaches may be combined in a single intervention requiring multi-disciplinary working of health care professionals, psychologists, social workers, teachers and sup-

TABLE 1

Overview of Psychological and Educational Interventions	
Psychological Interventions	
Behavioural interventions	The therapist uses behavioural therapy to modify the patient or carer's behaviour. For eczema habit reversal behavioural therapy is used to break the patient's habit of unconscious, repetitive scratching and also to develop less damaging behaviours when there is a real desire to scratch.
Relaxation techniques	Can be used to reduce stress and anxiety. There are many such techniques (also known as arousal reduction techniques). Two widely used methods are: • *Progressive relaxation*: teaches individual to tense different muscles groups in their body and then relax them. The individual becomes able to recognise areas of tension and to consciously release that tension. • *Visualisation* (or guided imagery): teaches the individual to use images associated with relaxation and calmness to purposefully induce these feelings in their own body Other relaxation techniques are *hypnotherapy*, *autogenic training* and *biofeedback*.
Psychological therapies	These are predominantly 'talking therapies' that enable people to develop improved insight into their problems and then change their thought processes, behaviour and coping style. *Cognitive behavioural therapy* uses a strong theoretical base to achieve these changes whereas in *counselling* a non-directive, non-judgemental approach is used to support the individual develop more effective ways to cope. *Family therapy* focuses on the family rather than the individual and facilitates discussion between family members of the challenges of coping with allergies, and together they develop improved strategies for change.
Educational interventions	
• Need to address the skills and confidence, as well as their knowledge, if they are to be successful • Can use a variety of instructional strategies (booklets, role play, problem solving, computer assisted instruction etc) • Can be delivered to individuals, to families or groups • Can be combined with psychological interventions for enhanced impact	

port groups. Many educational programs are based on "Social Learning Theory" and strive to improve self efficacy through improving knowledge, skills and confidence. A simple psychological technique such as relaxation might work in an eczematous patient by reducing anxiety and stress which exacerbate their perception of itch. In paediatrics, the interventions may be offered to the parents rather than to the allergic child. For example cognitive behavioural therapy may help parents of food allergic children develop new ways to deal with their stress and low mood. If successful, the therapy improves their quality of life as well as that of their allergic child.

Whilst patients report individual benefit from psychological interventions and some clinicians have case series supporting their use, we lack rigorous evidence about which interventions impact best on psychological distress, quality of life and symptoms. Despite this paucity of evidence adoption of a bio-psychosocial approach when developing a management plan ensures that the wider consequences of allergy are addressed.

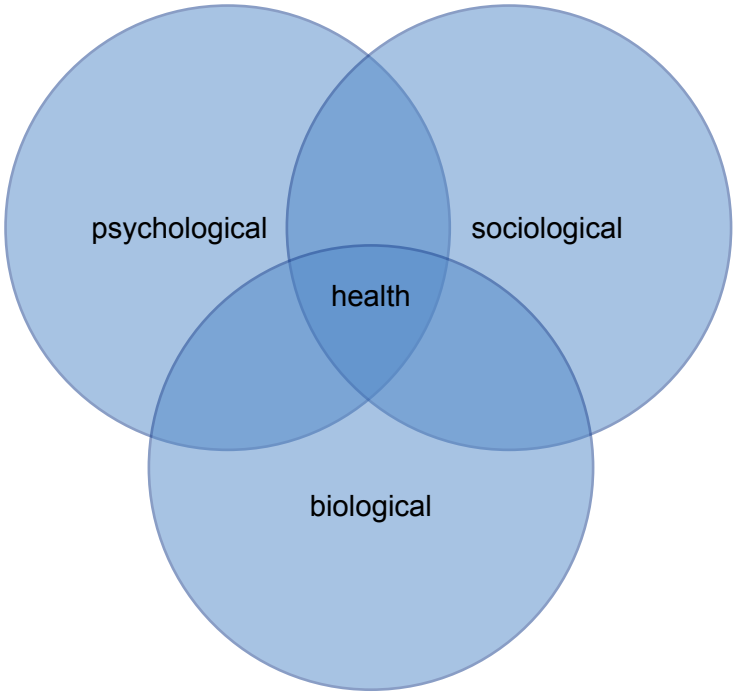

Figure 1 Bio-psychosocial model of health and illness. Psychosocial factors, including beliefs, relationships and mood, impact on patients' quality of life and ability to cope with their illness. Incorporating a holistic view in the consultation can ensure patient's wellbeing is addressed in its entirety.

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12 PHARMACOGENETICS AND PHARMACOGENOMICS OF ALLERGIC DISEASES

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KEY MESSAGES

- The current state of the art in pharmacogenetics/genomics of allergy is not yet predictive on a large scale, but provides a model for future study
- Pharmacogenetic profiling has been done mostly for asthma treatment, but also in the analysis of the response to treatment of other allergic diseases including rhinosinusitis, food allergy and atopic dermatitis
- Most of the studies of asthma pharmacogenetics have identified variability of responses to three classes of medications: inhaled and systemic glucocorticoids, leukotriene modifiers and beta adrenergic receptor agents
- A number of the genetic variants seen in the Th2 responses have been associated with severity and responses to treatment in chronic rhinosinusitis and in atopic dermatitis

Pharmacogenetics and pharmacogenomics of allergic diseases refers to the relationship between genotype and/or genetic variants, and the response to treatment (Table 1). Pharmacogenetic profiling in association studies has been done mostly for asthma, but also in some circumstances in the analysis of the response to treatment of other allergic diseases including rhinosinusitis, food allergy and atopic dermatitis.

Most of the studies of asthma pharmacogenetics have identified variability of responses to three classes of medications: inhaled and systemic glucocorticoids, leukotriene modifiers and beta adrenergic receptor (β2 AR) agents involved in bronchodilatation (Table 2). The demonstration that genetic variations influence FEV1 response to asthma treatment clearly supports the value of the pharmacogenetic approach to differentiate responders from non-responders. At this particular point, in time, the application of this approach in a widespread screening manner that would have meaningful implications for the treatment of asthma is somewhat hopeful and part of the future. The current state of the art in pharmacogenetics/genomics of allergy is such that it is not yet predictive on a large scale, but provides a model for future study.

There is no question that pharmacogenetics of glucocorticoids pathways has identified genetic variance that defines severity within the asthmatic populations together with differential responses to treatment with glucocorticoids. Genetic studies included in the asthma Childhood Management Program (CAMP) identified SNPs in the CRHRI gene associated with changes in FEV1 in response to inhaled glucocorticosteroids (ICS). Similarly, the genetic variance in the TBX2I gene identifies differences in the response to ICS in Asian population. Further studies identified variations in a number of genes including ORDML3 and cytochrome genes (CYP3A4, 3A5, 3A7) that correlate with the response to ICS. In addition, genetic variants within the low affinity IgE Fc receptor, CD23 or FcεR2, have also been associated with the variability of response to ICS in the CAMP study.

Pharmacogenetics of the β2 AR pathway has been of great inter-

TABLE 1

Definition for Pharmacogenetics/Pharmacogenomics
• Pharmacogenetics-Influence of genetic variants on treatment response in Allergy and Asthma
• Pharmacogenomics – Influence of genomic expression on treatment response in Allergy and Asthma

TABLE 2

Example of Allergy/Asthma Treatment Pathways in Pharmacogenetics	
Treatment Pathway	**Genetic Variants**
Beta-Adrenergic Agents	Beta-Adrenergic Receptors
Inhaled Corticosteroids	Inflammatory and Metabolic
Leukotriene Pathway agents	5-Lipoxygenase and LT receptors
Antihistamines	Histamine receptor variants
	Histamine pathway

est, because of the possibility of bronchodilator responses correlating with greater risk for asthma exacerbations and even mortality. A variety of studies have identified changes in Arginine and Glycine at position 16 of the β2 AR gene separating responders from non-responders to the bronchodilator effects of long acting beta2 agonists. On the contrary, the association of asthma severity and mortality with any of these genetic variants has proven illusive.

Cysteinyl leukotriene receptor genes also have been associated with asthma responses to treatment. In addition, variants in 5-lipoxygenase genes predict responses to the 5-lipoxygenase inhibitor Zileuton.

All of these responses in the various treatment pathways in asthma are clearly influenced by genetic variants that control drug treatments. Pharmacogenomics identifies multiple pathways of genes that might be activated in response to treatments. Several studies are undergoing, but the data is not available for publication as yet.

A number of the genetic variants seen in the Th2 responses have been associated with severity and responses to treatment in chronic rhinosinusitis and in atopic dermatitis (AD). Th2 genetic variants have also been identified as being potential contributors to AD, as well as a variety of genes including filaggrin that are important for the integrity of the epithelial barrier. In addition, a variety of genetic variants have been identified in the histamine pathway and receptor system that influence allergy.

FUTURE PHARMACOGENETICS APPROACHES

There is no doubt that selection responders to treatment based on genetic variants will eventually be an accepted clinical attribute. Given the successful example of the analysis of genetic pathways in tumors directing treatment for cancers, we can assume that within the next five to ten years the pharmacogenetic/genomic approach will began to be accepted as part of the overall assessment for asthma and allergic diseases.

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13 PHARMACOECONOMICS OF ALLERGIC DISEASES

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KEY MESSAGES

- Allergic diseases are amongst the most common and costly chronic conditions seen in westernized societies; both direct and indirect costs contribute substantially to disease burden
- Allergic rhinitis (AR) is the fifth costliest chronic disease in the U.S., with estimated direct costs exceeding $11 billion in 2005. The direct cost of AR in Europe are not known but was estimated at €1.0 to €1.5 billion in late 1990s
- Allergen immunotherapy (AIT) has a disease-modifying effect that can prevent the progression of AR to asthma, the development of new allergy sensitivities, and progression of disease severity
- These combined outcomes translate the clinical efficacy of AIT into a significant economic benefit. This economic benefit has been confirmed in a number of studies that have compared subcutaneous and /or sublingual AIT with standard drug treatment from several different perspectives e.g. societal, healthcare system or 3rd-party payer

Allergic respiratory diseases are amongst the most common and costly chronic conditions seen in westernized societies. Globally, allergic rhinitis (AR) is the most common allergic disease affecting approximately 500 million people world-wide, including an estimated 113 million in Europe and 30-60 million in the United States (U.S.) The prevalence rate of physician-diagnosed asthma was 4.3% in a 2002-2003 Global Health Survey, but varied by as much as 21-fold amongst the 70 countries surveyed. Both conditions can be associated with a number of symptoms and comorbid illnesses that can significantly contribute to the indirect costs of their treatment, e.g., cognitive dysfunction, daytime fatigue, sinusitis, and sleep disorders.

Allergic rhinitis is the fifth costliest chronic disease in the U.S., with estimated direct costs exceeding $11 billion in 2005. The direct cost of AR in Europe are not known, but was estimated at €1.0 to €1.5 billion in late 1990s.

The indirect costs associated with AR are considerable. In a survey of U.S. employees, the total annual cost of lost productivity attributable to AR was about $600 per employee (2002 value), which was significantly higher than the cost for any other condition assessed including diabetes and coronary heart disease. In Europe, the loss due to untreated AR-related presenteeism has been estimated to be approximately €100 billion (2011 value) annually.

While pharmacotherapy can be effective in controlling allergic symptoms, it does not address the underlying allergic cause. Efficacy requires ongoing treatment and the benefits are lost shortly after the medication is discontinued. In contrast, the efficacy of allergen immunotherapy (AIT) can persist long after discontinuation due to the induction of allergen-specific tolerance. In addition to reducing the need for long-term symptomatic drug treatment, AIT's disease-modifying effect can prevent the progression of AR to asthma, the development of new allergy sensitivities, and progression of disease severity.

TABLE 1A

STUDIES COMPARING SLIT WITH STANDARD DRUG TREATMENT (SDT)

STUDY	COMPARATORS	TYPE	PERSPECTIVE	RESULTS
Schadlich 2000	Pollen or HDM SCIT for 3 years plus SDT as needed; SDT	CEA	Society, healthcare system, 3rd-party payer	SCIT < SDT over ten years. Break-even point reached in the 7th year.
Petersen 2005	Grass or HDM SCIT for 3-5 years plus SDT as needed; SDT	CEA	Society	Direct cost: SCIT >SDT If indirect costs of sick days included in the economic evaluation, SCIT costs < SDT
Ariano 2006	Parietaria SCIT for 3 years plus SDT as needed; SDT	CCA	Healthcare system, society	SCIT < SDT; 80% cost reduction found 3 years after stopping SCIT
Keiding 2007	Grass SCIT for 3 years plus SDT as needed; SDT	CEA CUA	Healthcare system, society	SCIT cost-effectiveness per QALY; in the range of €10,000-25,000 per QALY from perspective of the healthcare system.
Omnes 2007	HDM or pollen SCIT 3 -4 years plus SDT as needed: SDT	CEA	Society	Cost-effective per incremental cost of asthma cases avoided (ICER)
Bruggenjurgen 2008	SCIT for 3 years plus SDT as needed; SDT	CUA	3rd-party payer, society	Break-even point =10 years. After 15 years -annual cost savings of €140 per SCIT-treated patient.
Hankin 2008	Costs 6 months before and 6 months after SCIT	CCA	Healthcare system	Weighted mean 6-month savings/patient: $401
Hankin 2010	SCIT for 18 months plus SDT as needed; SDT as needed for 18 months	CCA	Healthcare system	SCIT 18-month total healthcare costs 33% reduction compared with SDT
Hankin 2013	SCIT plus SDT as needed for 18 months; SDT as needed for 18 months	CCA	Healthcare system	SCIT 18-month total healthcare costs compared with SDT: Children: 42% reduction Adults: 30% reduction

These combined outcomes translate the clinical efficacy of AIT into a significant economic benefit. This economic benefit has been confirmed in a number of studies that have compared subcutaneous (SCIT) and /or sublingual immunotherapy (SLIT) with standard drug treatment (SDT) from several different perspectives e.g. societal, healthcare system, 3rd-party payer or some combination of these perspectives (tables 1A & IB). The analysis design employed in these comparative studies varied and included 'real-life' retrospective claims reviews and theoretical economic modeling (e.g., cost-consequence analysis). The outcomes assessed also ranged from 'real-life' total healthcare costs to theoretical Quality-adjusted Life Year (QALY) gained or number of asthma cases prevented. In some studies, cost-effectiveness was based on the presumption of persistent efficacy for years after discontinuation or prevention of asthma.

There was some variability across the studies in the AIT cost-effective or break-even time point. In a 6-year prospective study comparing a 3-year course of SCIT with SDT, the cost-savings became significant in the 3rd treatment year. AIT cost-savings reached 80% in the 4th year and was maintained through the 3 post treatment years. In some studies, the cost-effective 'time-point' was reached several years after discontinuation, which likely reflects the time required for the sustained benefits of AIT to outweigh the AIT treatment costs. However, in general, studies that collected costs via medical encounters or claims data demonstrated significant cost- savings during treatment. A 12-year retrospective claims analysis ('real-life' data), which included ~7.5 million people, found an 18- month total healthcare cost savings of 30% in adults and 42% in children with newly diagnosed AR, who received AIT compared with a matched AR population that did not receive AIT. This study confirmed the findings of a similarly designed pediatric study, that found progressive cost-savings that were significant 3 months after AIT initiation. These 'real-life' retrospective studies lend strong support for the cost-effectiveness of AIT.

TABLE 1B

STUDIES COMPARING SLIT WITH STANDARD DRUG TREATMENT (SDT)

STUDY	COMPARATORS	TYPE	PERSPECTIVE	RESULTS
Berto 2005	1 year of SDT before SLIT; SLIT for 3 years	CEA	Healthcare system, society	Cost-savings with SLIT per healthcare system and society: • Year before SLIT: mean annual healthcare costs/ annual total costs per patient were €506 and €2672, respectively • During SLIT: €224 (healthcare costs) and €629 (total cost)
Berto 2006	Pollen SLIT for 3 years plus SDT as needed; SDT	CCA	Healthcare system, society	SCIT compared to SDT: • Greater 6-year mean savings from payer and societal perspective. • More asthma cases avoided and patients improved
Bachert, 2007	Grass SLIT for 3 years plus SDT as needed; SDT	CUA	Society	SLIT cost-effective cost per QALY; average 0.0287 QALYs per season compared with SDT
Beriot-Mathiot, 2007	Grass SLIT for 3 years continuous or seasonal; SDT	CUA	Societal	Per ICER seasonal SLIT was cost-effective. Continuous SLIT was cost-effective if sustained effect for ≥2 years after treatment
Canonica 2007	Grass SLIT for 3 years plus SDT as needed; SDT	CUA	Society	SLIT cost-effective per QALY: average 0.0167 QALYs per season compared with SDT
Berto 2008	Grass SLIT for 1 year; SDT for 1 year	CCA	3rd-party payer	Mean annual direct costs for SLIT greater than SDT €311.4 and €179.8, respectively.
Nasser 2008	Grass SLIT for 3 years plus SDT as needed; SDT	CUA	Society	SLIT "very cost-effective" per QALY gained. QALY gained at 9 years = 0.197; equivalent to an extra "72 days of perfect health" for patients treated with SLIT when compared with those receiving placebo
Ariano 2009	SLIT for 3 years plus SDT as needed; SDT	CCA	Healthcare system	Healthcare costs greater for SLIT plus SDT in year 1, same in years 2 and 3, and significantly lower in years 4 and 5, compared with SDT
Ruggeri 2013	SLIT for 3 years plus SDT as needed; SDT	CEA	3rd-party payer, society	SLIT cost effective per ICER; benefit of 0.127 QALYs in patients with medium AAdSS and 0.143 QALYs in patients with high AAdSS.

CCA=cost-consequence analysis; CEA=cost-effectiveness analysis; CUA=cost-utility analysis; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SCIT=subcutaneous allergy immunotherapy; SLIT=sublingual allergy immunotherapy; SDT=standard drug treatment, HDM= house dust mite, AAdSS=adjusted average symptom score

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Section H

TOWARDS A COMPREHENSIVE GLOBAL STRATEGY FOR THE MANAGEMENTOF ALLERGIC DISEASES

* Contribution of allergy to the burden of non-communicable diseases
* Allergic diseases on the political agenda
* Policies and strategies to facilitate access to diagnosis and treatment for allergic diseases
* Policies and strategies to reduce risk factors for allergic diseases
* The role of primary care in the management of allergic diseases
* The role of allied health in the management of allergic diseases
* The role of patient organisations in the management of allergic diseases
* EAACI PAtient Organisations committee
* The role of pharmacists in managing allergic diseases
* The role of schools in managing allergic diseases
* Comprehensive allergy management plan. Towards a patient-centered attitude
* Social mobilization for management of allergic diseases
* Best buys for allergy prevention and control
* Dealing with the implementation gap for allergy prevention and control
* Generating resources for allergy prevention and control
* Strengthening the speciality of Allergology and Clinical Immunology
* EAACI-UEMS Exam in Allergology/Clinical Immunology
* Managing allergic diseases in developing countries
* The “One Health” concept and allergic diseases
* Allergy and active and healthy ageing
* Allergy in internet
* iCAALL: International Collaboration in Asthma, Allergy and Immunology
* Vision and roadmap to fight with allergies

1 CONTRIBUTION OF ALLERGY TO THE BURDEN OF NON-COMMUNICABLE DISEASES

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ASTHMA, RHINO-CONJUNCTIVITIS AND ECZEMA

Asthma, rhinoconjunctivitis and eczema are three prevalent non-communicable diseases, which are caused by allergy. They can result in limitation of activity and function and lower quality of life, particularly when they coexist together in the same individual. The prevalence varies between and within countries. Globally, the prevalence for current asthma, rhinoconjunctivitis and eczema in the 13-14-year age group has been reported to be 14.1%, 14.6% and 7.3%, respectively. In the 6-7-year age group the prevalence for current asthma, rhinoconjunctivitis and eczema has been reported to be 11.7%, 8.5% and 7.9%, respectively.

The data on the relationship between socioeconomic status and prevalence of these conditions have shown mixed results. Genetic and environmental factors play important aetiological roles. Those who suffer from asthma, rhinoconjunctivitis and eczema may also have a greater tendency to develop other allergies such as food and drug allergies. More research is needed to understand the aetiology of these allergic conditions.

KEY MESSAGES

- Asthma, rhinoconjunctivitis and eczema are three prevalent non-communicable diseases caused by allergy
- The majority of cases of allergic diseases can be diagnosed and managed in primary care, if there are functioning health systems, including access to essential medicines
- The WHO global action plan for prevention and control of non-communicable diseases 2013-2020 provides many policy options to bridge the gaps in diagnosis and treatment of major non-communicable diseases, including asthma
- Reducing premature mortality from chronic respiratory diseases, including asthma, can contribute to the global target of reducing premature deaths due to major non-communicable diseases by 25% by 2025

ALLERGY TO DRUGS, FOOD AND INSECT STINGS

Allergy to drugs, food and insect stings may present as acute urticaria, angioedema, dyspnoea and other symptoms of anaphylaxis in the skin, gastrointestinal, respiratory or cardiovascular systems. Anaphylactic reactions, although not common, may be fatal within minutes. Immediate drug reactions are seen most commonly with analgesics, antibiotics, radiocontrast media and muscle relaxants. Food items that can cause allergy include shellfish, peanut and egg.

PREVENTION AND TREATMENT

Anaphylaxis can be effectively treated, if there is access to emergency services including adrenaline injections. Prevention strategies include increased awareness of food and drug allergy, recording a history of drug allergy in all patients and stricter enforcement of food labelling laws. The majority of cases of asthma, rhinoconjunctivitis, eczema, drug and food allergy can be diagnosed and managed in primary care, if there are functioning health systems, including access to essential medicines.

Deaths and hospitalization due to asthma in resource-constrained

settings are usually a consequence of weak health systems. The WHO global action plan for prevention and control of noncommunicable diseases 2013-2020 provides many policy options to bridge the gaps in diagnosis and treatment of major noncommunicable diseases, including asthma. Reducing premature mortality from chronic respiratory diseases including asthma can contribute to the global target of reducing premature deaths due to major noncommunicable diseases by 25% by 2025.

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2 ALLERGIC DISEASES ON THE POLITICAL AGENDA

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KEY MESSAGES

- The rapid increase in the prevalence of allergic diseases has driven Allergology as a medical specialty, and provided plentiful material for research
- The activities of the EAACI have been pivotal for prioritizing allergic diseases in the European political agenda
- The 'Global Allergy and Asthma European Network (GA2LEN) developed into a EU flagship program bringing together an impressive number of European Institutions, resulting in hundreds of scientific publications and at least two 'spin-off' projects, MEDALL and PreDicta
- Following the proposal of the Polish EU Presidency in 2011, the European Council formally recognized the chronic respiratory diseases, including allergies, as major disease priorities
- The Written Declaration on the burden of allergic diseases achieved considerable interest and 178 Members of the European Parliament signed the Declaration

Allergy is a modern concept. Despite the occasional case reports, allergic diseases were rare just until a century ago. Since then and parallel to major changes in life-style, allergic diseases have become a major epidemic: in some countries, more than half of the population is already sensitized to allergens, while >30% suffer from one of more allergic diseases.

This rapid increase in prevalence has driven Allergology as a discrete domain and medical specialty, and provided plentiful material for research, discovering the immunological basis and systemic nature of allergy and bringing together allergy with clinical immunology. Allergy research remains a key need, for symptom control, understanding and prevention.

The study and practice of allergy started in Europe in the beginning of the 20th century, stemming from developed disciplines where allergic symptoms were more frequent or more evident. Interestingly, quite diverse schools developed in different countries, generating 'traditions' with equally diverse prioritization and political direction in relation to allergy research and health services. Such diversity remains in Europe, where some countries consider Allergology as a full medical specialty, while others as a subspecialty; in some cases there is no formal recognition, while integration with Immunology is equally diverse. Some countries, with the pioneering example of Finland, have established National Programs in allergy and asthma, with tangible results.

The activities of the European Academy of Allergy and Clinical Immunology (EAACI) have been pivotal for prioritizing allergic diseases in the European political agenda. This has been achieved in several occasions, although not yet consistently. The support within the EU Framework Program (FP) 6 of the 'Global Allergy and Asthma European Network (GA^{2}LEN), was a notable success, following EAACI presence and lobbying in Brussels. GA^{2}LEN developed into a EU flagship program and has achieved sustainability, bringing together an impressive number of European Institutions, resulting in hundreds of scientific publications and at least two 'spin-off' projects,

Figure 1 GA²LEN is both a result and a driver of the European research agenda in relation to allergies.

Figure 2 Prof. Nikolaos Papadopoulos addressing the Polish EU Presidency. The EU Council Conclusion suggested continuous investment in chronic respiratory diseases including allergies.

Figure 3 The EAACI Campaign supporting the Written Declaration on the burden of allergic diseases led to considerable appreciation among MEPs.

MEDALL and PreDicta, embedded in the FP7 framework (Figure 1).

Another milestone was the formal recognition by the European Council of chronic respiratory diseases, including allergies, as major disease priorities, after the proposal of the Polish EU Presidency in 2011 (Figure 2).

Realising the need for consistent presence and involvement in EU and international political fora, EAACI has recently reinstated a Brussels Office. As the major partner and backing force to a proposal by Members of the European Parliament (MEPs) for a Written Declaration on the burden of allergic diseases, considerable interest was generated and 178 MEPs signed the Declaration (Figure 3).

Looking into the future, prioritization of allergic diseases will come through partnerships with organisations seeking similar goals in the field of health and research. It is clear that allergies share most of the major risk factors with other chronic non-communicable diseases. A global approach, familiar to those who deal with allergy, needs to consider all chronic diseases and the lifestyle changes necessary to improve overall health of the population.

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3 POLICIES AND STRATEGIES TO FACILITATE ACCESS TO DIAGNOSIS AND TREATMENT FOR ALLERGIC DISEASES

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The world is in the midst of an allergy and asthma epidemic. This has resulted in an unmet need to increase in accessibility of allergy services for those who need it delivered by those who have the expertise to provide it. Late diagnosis and wrong diagnosis of atopic disorders often results in increased morbidity, increased mortality, and increased resource utilization, all of which may result in suboptimal outcomes for patients, who suffer from these disorders and for institutions that are responsible for bearing much of the cost for managing these disorders. One of the fundamental questions that healthcare providers and institutions are pondering is what strategies can be implemented to facilitate access to diagnosis and treatment of allergic disorders in a timely manner that will decrease morbidity and mortality associated with allergic diseases, decrease resource utilization associated with these diseases, and improve quality of life for the individuals suffering from these allergic disorders.

KEY MESSAGES

- There is an unmet need to increase the accessibility to allergy and immunology services by those who need it delivered and by those who have the expertise to provide it
- No uniform policies and strategies for increasing accessibility to these services will be applicable in all circumstances
- Healthcare coverage and a source of usual care together, better satisfy this unmet need than either healthcare coverage or a source of usual care alone
- Patient centered medical homes with allergists serving as neighbor participants, coordinated care, timely referral to an allergist, and utilization of connect health options can improve and expand access to allergy and immunology care

VARIABILITY IN HEALTHCARE ACCESS AND COVERAGE

The highly affluent have few challenges accessing top quality healthcare. Access to asthma and allergy care will vary based on one's socioeconomic status, based on the country within which one lives, and based on the availability of trained individuals to provide such care. The variable financial coverage for healthcare in different parts of the world make it clear that one size does not fit all, when it comes to healthcare delivery policies and strategies. Consequently, no uniform policies and strategies will be universally applicable to all people in all locations in the world. However, some basic principles may be universally applicable as strategies for improving access to healthcare in order to facilitate early diagnosis and early medical and environmental interventions for the treatment of allergic diseases.

HEALTHCARE COVERAGE IS NOT EQUAL TO A SOURCE OF USUAL CARE

Several scholars have pointed out the importance of both health insurance, public or private, and a source of usual care as important facets of healthcare accessibility that are, in part, dependent on one's socioeconomic status. There are obvious advantages of each. Consequently, any strategy to increase access to allergy and immunology healthcare in order to

TABLE 1

Approaches to improve access to allergy and immunology services
1. Include allergists as neighbor participants to provide allergy and immunology services for complex cases in patient-centered medical homes.
2. Use access to care "coordinators" to recruit allergy patients and to arrange and coordinate their allergy care.
3. Educate primary care providers about when referral to an allergist is necessary and encourage the concept of co-management of complex allergic diseases by these providers with allergists.

TABLE 2

Connected health options to expand access to allergy and immunology care
1. Utilize tele-health technology to allow allergists to provide selected allergy and immunology services virtually anywhere, including primary care provider offices, prisons, and remote areas.
2. Provide asthma screening and management via telemedicine video conferencing appointments.
3. Provide asthma and allergy monitoring and reporting via medical apps for smart phones and tablets.
4. Use web-based communication technology and portals to provide patients with automated alerts and important feedback after they have been diagnosed with asthma and allergic diseases.

facilitate early diagnosis and early interventions should promote both healthcare coverage and a usual and consistent source of healthcare. Data indicate that, compared with patients having both health insurance and a regular source of care, insured patients without a usual source of care have higher rates of unmet medical needs and problems obtaining specialty care. The converse is very worthy of note. Having no health insurance, but having a regular source of healthcare predicts a higher likelihood of being unable to get timely urgent care, prescriptions, and needed health counseling. Getting specialty care has more to do with having a usual source of healthcare, (and with the characteristics of that usual source).

In many parts of the world, it has become clear that having public or private insurance does not necessarily guarantee the ability to obtain needed allergy and immunology services if there is no usual source of healthcare.

Actual receipt of care is clearly more important than access to healthcare. Therefore, any policies and strategies to improve allergy and immunology healthcare services must ensure that these services are delivered and that non-allergy specialists are educated about when such services are needed. The take home point is that healthcare coverage facilitates having a usual source of care, but it is the usual and regular source of care that can facilitate the provision of allergy and immunology services when they are needed.

WAYS TO IMPROVE AND EXPAND ACCESS

Despite their valiant efforts, healthcare researchers to date have not yet universally influenced policy makers to implement ideal strategies that will facilitate early diagnosis and early interventions for many allergic and immunologic diseases. Table 1 lists some useful approaches to improve access to allergy and immunology services. Table 2 itemizes some connected health options that could expand access to allergy and immunology care.

PATIENT CENTERED MEDICAL HOMES AND ACCOUNTABLE CARE ORGANIZATIONS

In the United States, there has been a grand movement towards patient centered medical homes (PCMH) governed by a primary care provider with allergists serving as neighbors to provide allergy and immunology services. Many PCMH operate under the auspices of large medical agencies called accountable care organizations (ACOs). ACOs are healthcare delivery systems that implement a team approach to coordinated care and provide high-quality healthcare at lower cost for large populations.

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4 POLICIES AND STRATEGIES TO REDUCE RISK FACTORS FOR ALLERGIC DISEASES

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KEY MESSAGES

- Reduce risk factors especially environmental pollutants, improve nutrition, physical activity, increase tolerance
- Increase capacity building and improve health care delivery, increase accessibility and affordability to treatment
- Raise the priority of allergic diseases at the level of governments, policy makers and the general public
- Establish and strengthen national policies and plans to promote interventions to treat and to reduce the burden of allergic diseases
- Support research that focuses on the increasing tolerance, early intervention and prevention and control of allergic diseases

A GLOBAL HEALTH PROBLEM

The prevalence of allergic diseases is increasing worldwide, both in developed and developing countries, in parallel with other chronic noncommunicable diseases (NCDs) and together comprise a major global public health challenge. The above include life-threatening anaphylaxis, food allergies, certain forms of asthma, rhinitis, conjunctivitis, angioedema, urticaria, eczema, eosinophilic disorders, including eosinophilic esophagitis, and drug and insect allergies. This increase is especially problematic in children, who are bearing the greatest burden of this rising trend, which has occurred over the last two decades. In addition, the complexity and severity of allergic disorders, including asthma, continues to increase, especially in children and young adults.

This upsurge in the prevalence of allergies is seen as societies become more affluent with change in life styles, dietary habits and better hygiene. Additional factors, like physical activity, nutrition, pollutants (both outdoor and indoor air pollution), climate change reduced biodiversity, gene-environmental interactions, epigenetic modulation and the microbiome all influence the immune system with chronic inflammation being the core underlying common factor (Figure 1).

POLICIES AND STRATEGIES

The challenge to reduce the burden of these diseases needs a multifactorial and multidisciplinary approach involving several stakeholders including specialists, scientists, governments, policy makers, patients, the public, health care professionals as well as industry.

Some simple interventions like physical exercise, a healthy diet and connection with the natural world and countryside are among potential ways to tackle this global health issue. Early interventional strategies through environmental control measures, evidence-based nutritional interventions that could potentially include probiotics, prebiotics or Vitamin D etc, or interventions like allergen immunotherapy that could strengthen immune tolerance are key elements for allergy prevention (Figure 2). At the same time the complexity of allergic diseases and asthma as identified from new research highlights the need of a more stratified and personalized approach to treatment like the use of newly emerging biologics and biosimilars.

In addition, global epidemiological

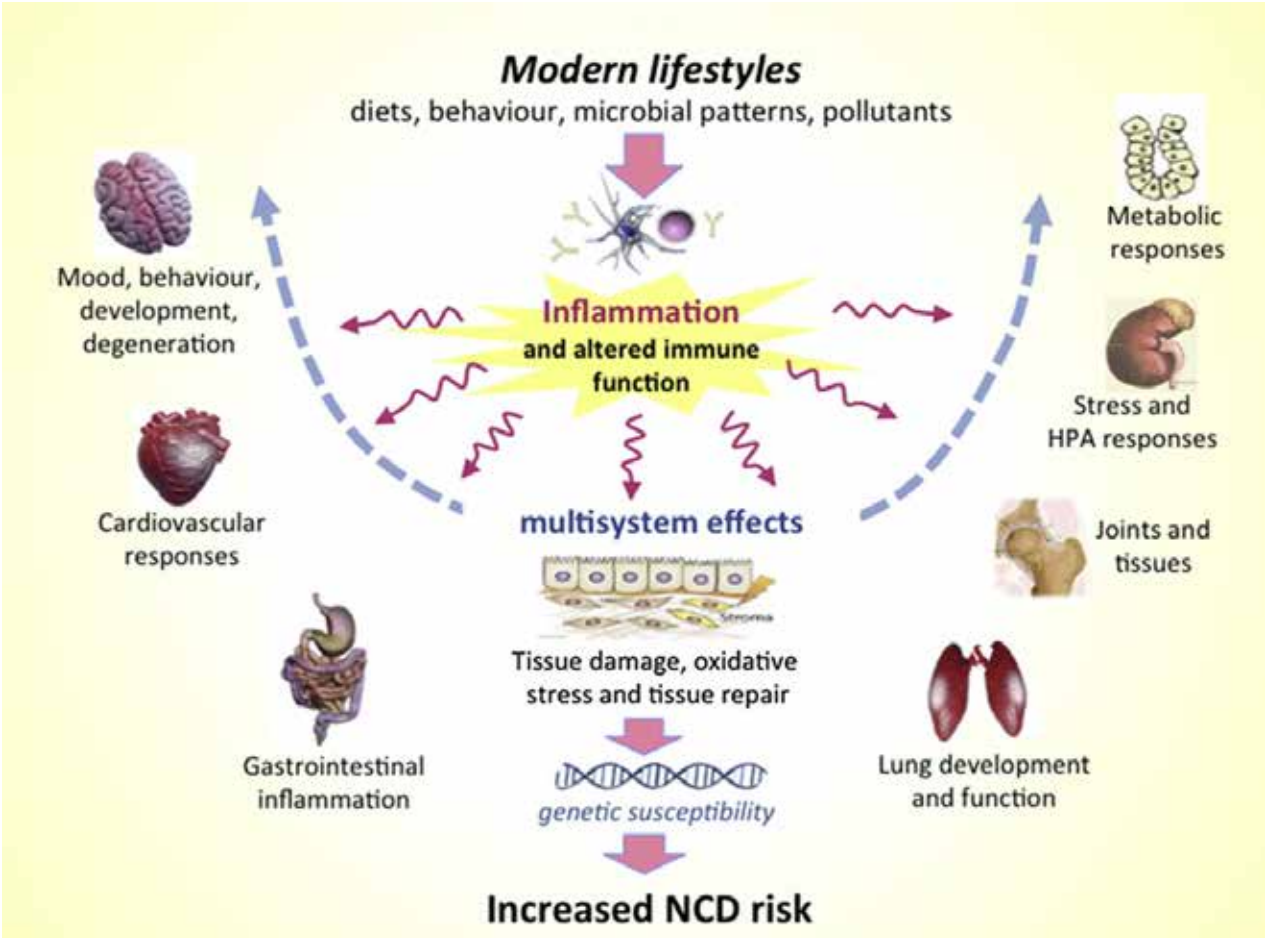

Figure 1 Common risk factors for allergic diseases and noncommunicable diseases. *(Reprinted from J Allergy Clin Immunol, 131/1, Prescott SL. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases, 23-30, Copyright 2013, with permission from Elsevier.)*

studies, increasing capacity building, increased global research on allergic diseases, especially on preventative strategies and early life interventions, collaborative action among academic organizations and inter-disciplinary cross talk, together with comprehensive, well defined nationwide action plans are needed. National action plans should target to reduce the risk factors, especially environmental pollution both outdoor and indoor, develop strategies to increase tolerance and improve nutrition and health. These action plans should be based on both scientific evidence and a broad clinical experience. The World Allergy Organization (WAO) has taken steps in this direction with the WAO White Book on Allergy, which provides a comprehensive view of the problem, includes reports from its national member societies about the current state of allergy/immunology resources in their countries, and offers recommendations for action.

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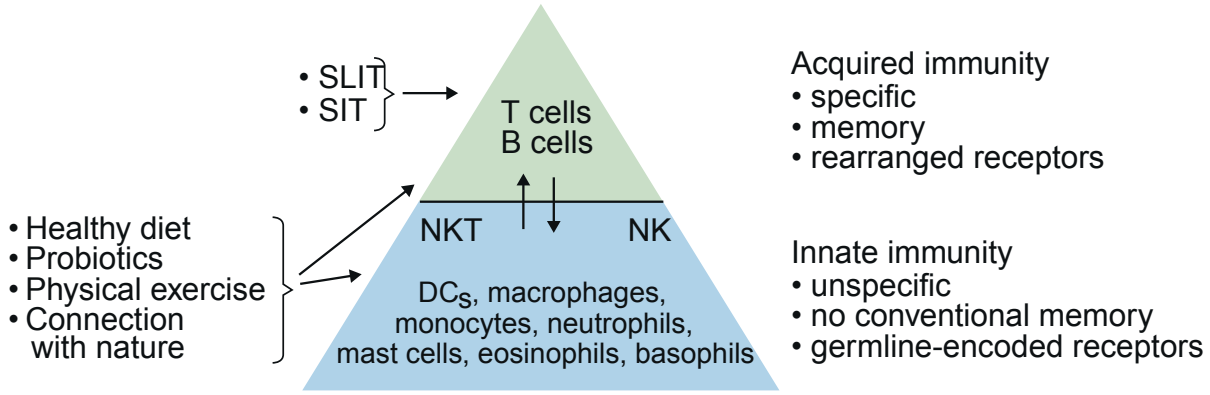

Figure 2 Induction of tolerance as a key strategy towards prevention. (*From Haahtela T, Holgate S, Pawankar R,et al; WAO Special Committee on Climate Change and Biodiversity. The biodiversity hypothesis and allergic disease: world allergy position statement. World Allergy Organ J. 2013;6:3.; Reprinted with permission under the Creative Common Attribution License or equivalent*)

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5 THE ROLE OF PRIMARY CARE IN THE MANAGEMENT OF ALLERGIC DISEASES

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KEY MESSAGES

- The first port of call for patients is usually the primary care or general practitioner (GP)
- GPs should determine whether the problem presented is allergic or non allergic in nature
- Most allergic disorders have the potential of being managed in primary care
- Stratification of severity should facilitate appropriate referral to specialists
- There is a need for further research into how care delivery can be optimised

The global population has crossed seven billion and increasing rapidly with just over 8.7 million physicians to meet their needs, with variability of less than 0.5 to 64 physicians per 10,000 head of population. A conservative estimate of the global prevalence of allergy in whatever form, is in the region of 20%: successive studies from differing locations all suggest that the prevalence is constantly increasing with little evidence of plateauing. The number of allergists available to meet this challenge is not known but range between 1:17,000 (Czech Republic) and 1:50 million (Pakistan), with figure in the region of 1:1 million for countries such as France, Turkey and the UK. With the paucity of trained allergists in low- and middle-income countries, the importance of the Primary Care Physician (PCP)/General Practitioner (GP) for diagnosis and management of allergic diseases is greatly heightened (Figure 1).

The first port of call for those who believe they are suffering from allergy is usually the general practitioner or family physician (Figure 2).

The symptoms may be clear and straightforward, which facilitates ease of diagnosis and management, but on the other hand may be more vague and poorly differentiated. Furthermore, many syndromes have allergic (IgE mediated) as well as non allergic aetiology. Elucidating the pathophysiology of the syndrome facilitates appropriate management, thus with regards to allergy management, the first critical step is to decide whether the presenting complaint(s) represents an allergic or a non allergic disorder.

In the primary care environment, many patients present with poorly defined symptoms, but with a stated belief that their symptoms are due to an allergy; it is the task of the physician to determine whether there is any medical basis for these symptoms or whether the patients suffer from medically unexplained symptoms/somatisation. The actual prevalence of allergic disease is considerably less than the number of patients who believe that they may have an allergy. With regards to food allergy this difference amounts to some 30% of people believing they have a food allergy with only in the region of 3% having this confirmed.

Thus, with regards to allergy management the first critical step is to decide whether the presenting complaint represents an allergic disorder. The challenge facing GP's is confounded further by various parties exploiting patient's worries fears and anxieties, deploying spurious investigations

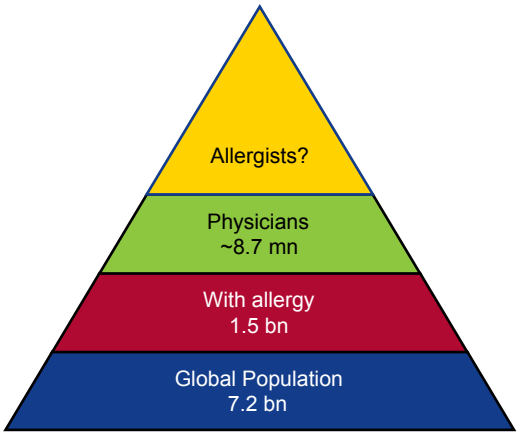

Figure 1 A schematic of the global population, the numbers of allergy sufferers and the medically qualified staff to meet these needs.

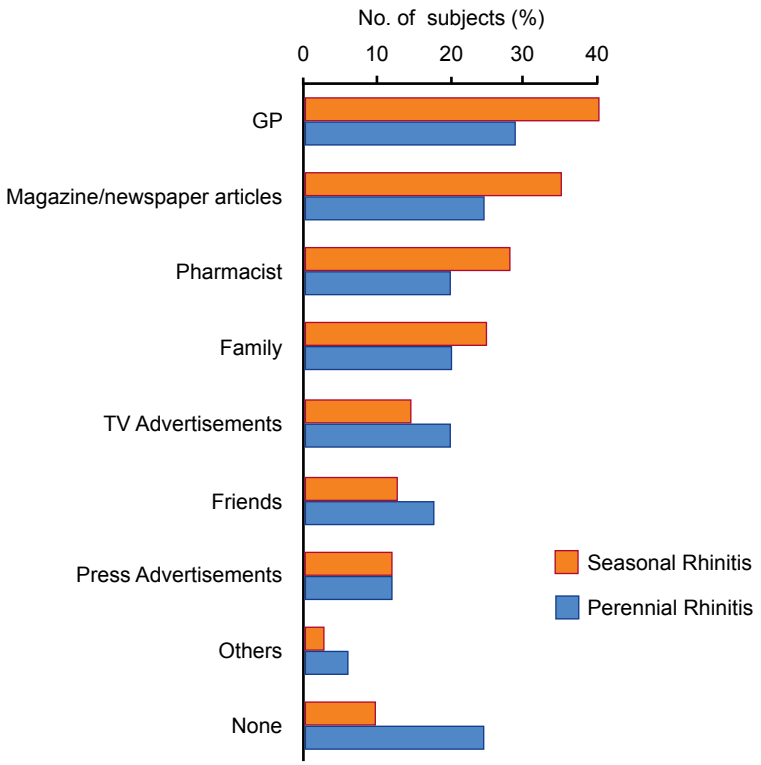

Figure 2 Sources of Information for patients for diagnosis and management of allergic rhinitis. (*Reproduced with permission from Scadding G, Richards D, Price M. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. Clin Otolaryngol Allied Sci 25:551–557, 2000.*)

to confirm diagnosis and equally spurious remedies to rectify the identified problem.

The big challenge then is to provide a service to patients so that their needs may be met in the most appropriate and expeditious manner. To facilitate this PCPs/GPs will need to be properly trained and equipped with the skills to recognise and manage straightforward allergy problems and to stratify them into those which may be safely and effectively managed in primary care, and also to identify those patients who need specialist assessment such as those who require challenge tests, allergen immunotherapy or management of anaphylaxis or food allergy.

The need and priorities for research into best practices for diagnosis and management of allergy and asthma in primary care have been detailed by the International Primary Care Respiratory Group (IPCRG) in a global Delphi exercise and highlighted by the European Academy of Allergology & Clinical Immunology (EAACI) by the creation of a PC Interest Group.

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6 THE ROLE OF ALLIED HEALTH IN THE MANAGEMENT OF ALLERGIC DISEASES

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KEY MESSAGES

- The development of allergy expertise within the dietetic profession is in its infancy in many countries, while the allergy and asthma nurse are more and more acknowledged in their central role in patient care in Europe
- The cornerstone of the treatment of food allergy is the proper avoidance diet, eliminating only the demonstrated offending foods while keeping a balanced nutrition and avoiding unnecessary restrictions
- Over the past decades, allergy and asthma nurses have developed skills in allergy diagnostics, such as skin-prick testing, spirometry and food challenges. More recently, they were involved in clinical trials
- Allied Health professionals in allergy act as link and central point between patient, physician and other healthcare professionals to ensure that the patients fully understands their diagnosis and treatment and that communication between all parties is maintained

The EAACI has always supported the involvement of Allied Health, and in 2010 the "EAACI Allied Health Interest Group" was formed.

DIETITIANS

Within Europe, the development of allergy expertise within the dietetic profession is in its infancy in many countries. There clearly is a great need for more practically and scientifically trained allergy specialist dietitians.

The cornerstone of the treatment of food allergy is the avoidance diet. Therefore, dietary management by the dietitian starts at the beginning of the diagnostic phase to ensure that an appropriate avoidance diet is composed. In some countries dietitians are trained to take an allergy focused diet history with the aim to link symptoms to foods causing symptoms and to determine nutritional status and deficiencies (Figure 1). In other countries dietitians are only involved in the dietary management of avoidance diets.

Avoidance diets can have a serious impact on quality of life and may lead to deficiencies and impaired growth due to extensive eliminations (Figures 2 and 3). Nutritional counselling by a dietitian is an essential prerequisite to ensure optimal relief of symptoms, prevent inadvertent exposure, prevent unnecessary avoidance, and support normal growth and development in children and to provide a healthy and balanced diet. In the dietary management plan, issues such as label reading, high-risk foods, eating out, school meals, day care, birthday parties, holidays, business and holiday travel and other social circumstances should also be addressed to limit the burden of the avoidance diet as much as possible.

NURSES

The role of the allergy nurse is extremely important. Nurses are a valuable asset in chronic disease management, and with appropriate training and competency assessment can provide a high standard of care. Studies in asthma and other chronic diseases have shown positive outcomes for patients and improvement in the management of a patient's condition with the support of a clinical nurse specialist. Over the past decades, nurses have developed skills in allergy diagnostics, such

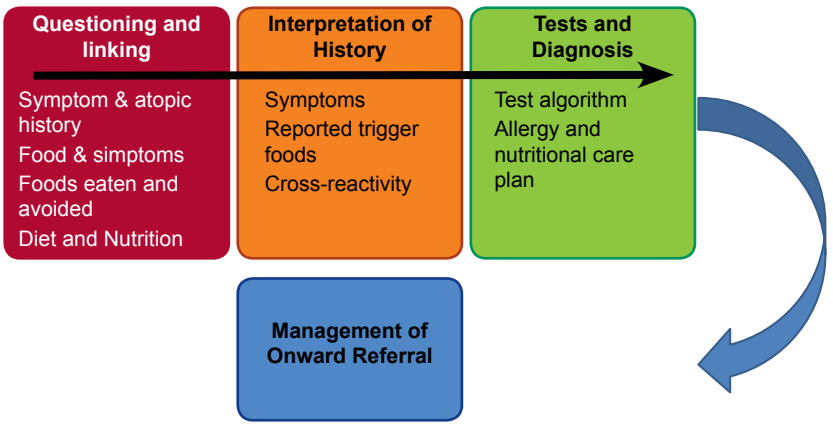

Figure 1 Allergy focused diet history tool for children and adults, currently under development by an Allied Health Task Force of the EAACI (red - wait and gather information; Amber – get ready to go by linking that information together to formulate a potential diagnosis; Green - the way ahead is clear to undertake further relevant tests).

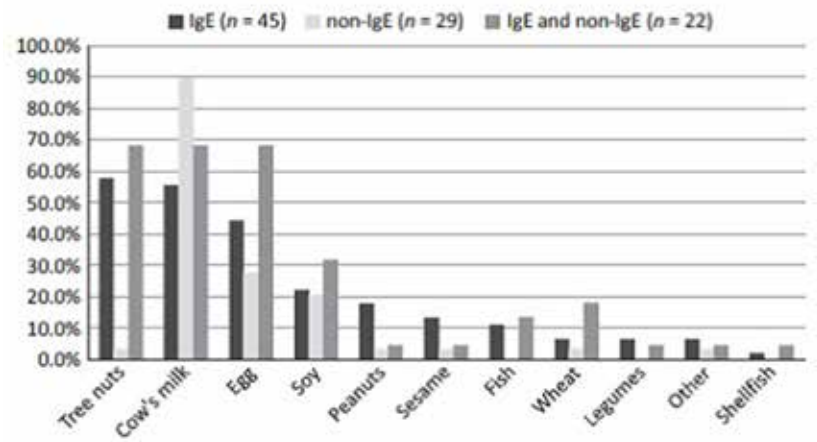

Figure 2 Summary of the most common food allergens excluded by the diet stratified by immunoglobulin (Ig)E, non-IgE and mixed IgE and non-IgE-mediated food allergies.

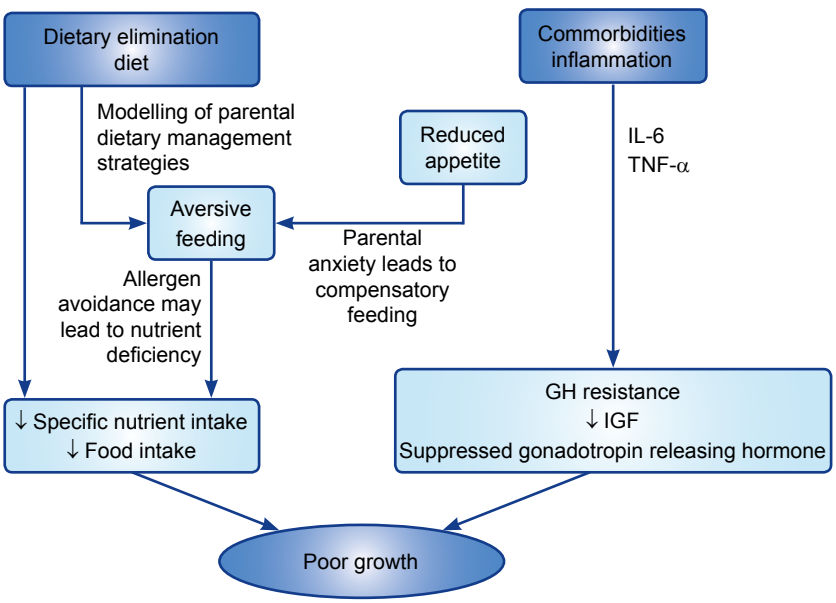

Figure 3 Proposed model for the development of malnutrition in the allergic child. IGF, insulin-like growth factor, IL, interleukin; TNF, tumor necrosis factor.

as skin prick testing, spirometry and food challenges. More recently competencies have been developed and are in-development in order to standardise care and practice. Nurse specialists in allergy act as link and central point between patient, physician and other healthcare professionals to ensure that the patients fully understands their diagnosis and treatment and that communication between all parties is maintained. Many nurses across the world are heavily involved into the implementation of treatment of allergic diseases. Increasingly they are also involved into allergy and asthma research.

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7 THE ROLE OF PATIENT ORGANISATIONS IN THE MANAGEMENT OF ALLERGIC DISEASES

EAACI Patient Organisation Committee

KEY MESSAGES

- Patient organisations traditionally provide peer support, information and education for patients and their carers to cope with their disease
- Patient organisations revolutionised advocacy and consequently the political impact of patient organisations grows as they strive for action and change as indicated, with the inclusion of patient representatives in official bodies advising on health, care and research policies
- The concept of the patient as an 'expert of experience' has developed aiming to provide input into research and healthcare using his or her unique expertise – first-hand experience of a disease
- The EAACI Patient Organisation Committee offers a well-organised and sustainable platform for communication and guidelines, enabling mutually beneficial interactions between patients and clinicians

Patient organisations traditionally provide peer support, information and education for patients to support their journey through the health care system. Patient organisations aim to promote prevention, and improve the quality of life for people affected by health conditions and for their families, through patient participation and empowerment.

The historic role for patient organisations in allergy, like in other diseases is to share patient's experiences and nowadays this is still a crucial function. Today, this exchange is also expanded through partnerships to allergy health care professionals, like allergists, second and primary care and support services like dieticians and policy makers at all levels. Within these partnerships, educational sessions are organised to help patients understand their condition and to empower them, so they can engage as a full partner in the societal activities they want to activitely participate in (Figures 1 and 2).

Globalisation and information technology are a great opportunity and challenge for patient organisations. Patients increasingly interact online and although many patient organisations still provide comprehensive and clear information on paper this is being supplemented with websites, videos, apps and social media. Here, patients and carers can get information and post their hopes for the near and distant future, while sharing their fears. Grasping this communication opportunity patient organisations revolutionised advocacy (Figure 3) and consequently the political impact of patient organisations grows as they strive for action and change as indicated, with the inclusion of patient representatives in official bodies advising on health, care and research policies.

Patient organisations are also playing an increasingly key role in funding national and international research. Public and patient involvement in European projects has become a key requirement in decisions for funding.

EAACI has installed a "Patient Organisation Committee" to ensure the input of allergic patients in their activities. This resulted for instance in the identification of patients' needs for partnership

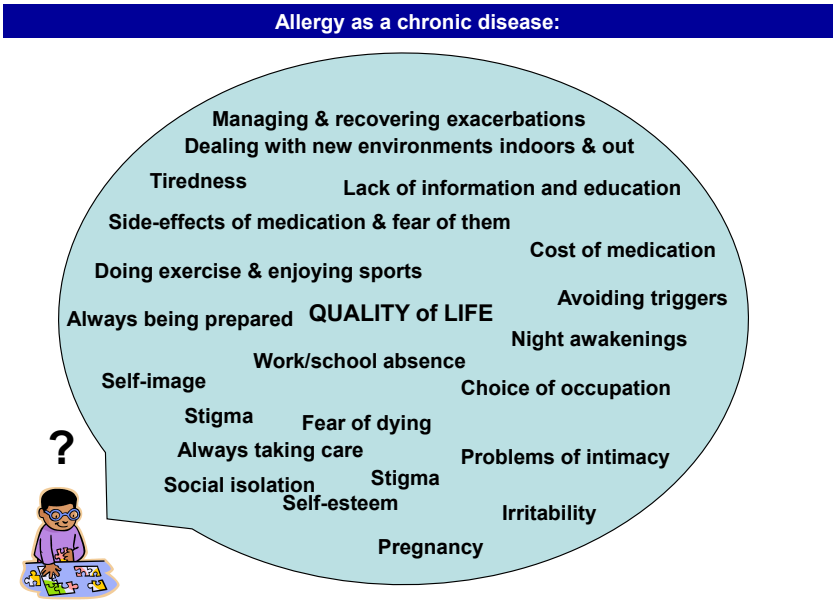

Figure 1 Explaining to patients the concept of allergy as a chronic disease.

Figure 2 Adrenaline auto-injector training.

Figure 3 Patient representatives advocate for better allergy care at the EU Parliament.

in clinical trials. Moreover, it led to a well-organised and sustainable platform for communication and guidelines, enabling mutually beneficial interactions between patients and clinicians.

The concept of the patient as an 'expert of experience' has developed. The expert patient aims to provide input into research and healthcare using his or her unique expertise – first-hand experience of a disease. Patient organisations have developed processes and methodologies to ensure that their members are fully prepared for involvement in areas like research and clinical trials, while ensuring patients are available to participate wherever needed. We all need to work together as allergy is a major public health problem!

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EAACI PATIENT ORGANISATIONS COMMITTEE

aha! Center for Allergy Switzerland

Allergy India

Allergy New Zealand Inc

Anaphylaxis Australia Inc

Anaphylaxis Canada

Anaphylaxis Ireland

Anoiksi NGO

Asociacion espanola de alergicos a alimentos y latex

Association Francaise pour la Prevention des Allergie (AFPRAL)

Association québécoise des allergies alimentaires

Deutscher Allergie und Asthmabund eV

European Federation of Allergy & Airway Diseases Patients Association

Food Allergy Italia

Food Allergy Research & Education

Fundacion Creciendo con Alergias Alimenarias

Prevention des Allergies A.S.B.L.

S.O.S Alergia

Swedish Asthma and Allergy Association

The Allergy Society of South Africa

The Anaphylaxis Campaign UK

The European Anaphylaxis Taskforce CV

The Hong Kong Allergy Association

Yahel Food Allergy Network Israel

8 THE ROLE OF PHARMACISTS IN MANAGING ALLERGIC DISEASES

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Viktor Hafner
Austrian Pharmasist Association, Austria

Otto Spranger
Austrian Lungenunion, Wien, Austria

KEY MESSAGES

- Allergic diseases are frequently under diagnosed and many patients tend to use unproven means to relieve their symptoms
- Pharmacists are often the first healthcare professionals seeing a person at risk of an allergic disease
- Many pharmacy-based studies demonstrated that pharmacists are able to identify, counsel and refer to a physician patients with previously undiagnosed chronic conditions, including type 2 diabetes, cardiac diseases, COPD and uncontrolled asthma
- Pharmacists can successfully provide screening for people at risk of allergic diseases and motivate at-risk subjects to consult a physician to receive an early and correct diagnosis and treatment

The symptoms of respiratory allergies are distressing and negatively impact on the patient's quality of life. However, many patients with respiratory allergy do not recognise their condition and fail to consult a physician. In a study of over 9000 people in Europe, Bauchau et al. found that the prevalence of subjects with clinically confirmable allergic rhinitis ranged from 17% in Italy to 29% in Belgium, with an overall prevalence of 23%. However, surprisingly, 45% of these subjects had not been previously diagnosed by a physician.

Many patients tend to use unproven means to relieve their symptoms, usually without a proper diagnosis. Given the availability of over-the-counter reliever medications for allergy symptoms, pharmacists are often the first healthcare professionals seeing a person at risk of an allergic disease. Consequently, they are in a good position to identify patients at risk of allergy.

In this context, community pharmacists can be considered a valuable component of the primary healthcare team, and can play a major role in the early identification of the condition and guide patients to a correct diagnosis. Many pharmacy-based studies demonstrated that pharmacists are able to identify, counsel and refer to a physician, patients with previously undiagnosed conditions, including type 2 diabetes, cardiac diseases, COPD and uncontrolled asthma.

Recently, the role of pharmacists in the early identification of customers with respiratory allergy was evaluated in a pilot study, conducted by The European Federation of Allergy and Airways Diseases Patients Associations (EFA) in collaboration with the Pharmaceutical Group of the European Union, the Austrian Pharmacists Association and the Austrian Lungenunion. Between April and June 2013 (high allergy season in Austria), pharmacists in 315 pharmacies in Vienna were invited to evaluate the allergy risk of customers with symptoms of respiratory allergy or asking for over-the-counter treatment for allergic symptoms, using the validated Allergy Screening Test ASF Questionnaire. A total of 2297 questionnaires were completed. Of these 76% were at a moderate-severe risk of allergy (Figure 1), although only 35% of the total had been tested for allergy. Of the 1486 participants that were never tested for allergy, 68% were at high risk of allergy (Figure 2) and 57% "clearly felt unwell" because of their symptoms (Figure 3). Pharmacists advised 49% of their

customers to consult a physician for their allergic risk.

Screening and case detection are a part of prevention strategies that seek to identify and limit complications associated with chronic conditions. Screening for allergies may improve the quality of life of patients by promoting early diagnosis and appropriate treatment and therefore preventing exacerbations or life-threatening episodes due to severe anaphylaxis or severe asthma. Based on the results of the above pilot study, pharmacists can successfully provide screening for people at risk of allergic diseases. In addition, they can play a role in motivating at-risk subjects to consult a physician to receive an early and correct diagnosis and treatment and overall improve patients' quality of life.

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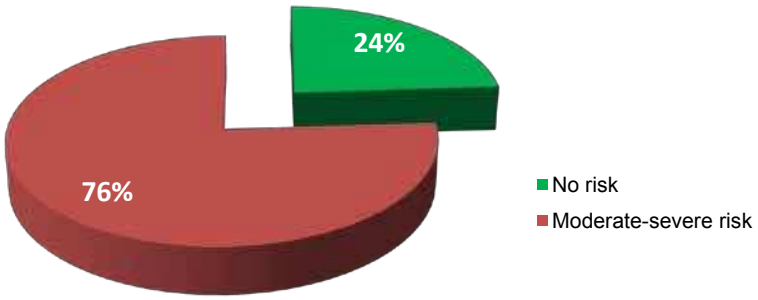

Figure 1 Participants at a moderate-high risk of allergy (n. 2297) .

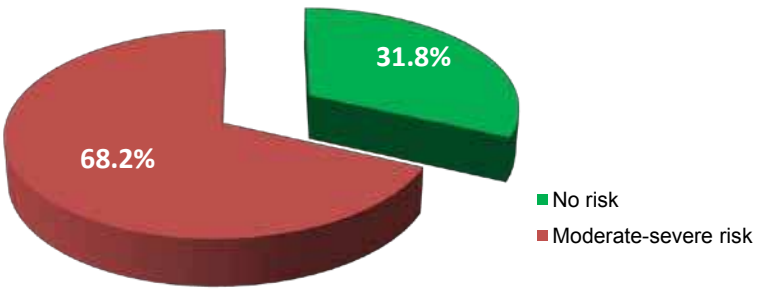

Figure 2 Risk of allergy in participants who never had allergy test (n.1486).

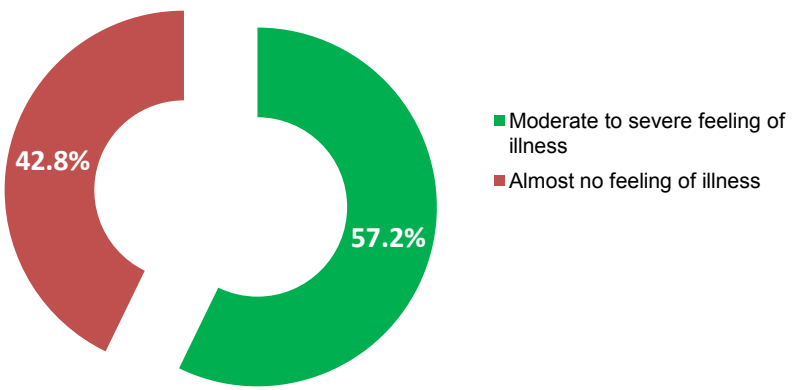

Figure 3 Feeling of illness in participants who never had an allergy test (n. 1486).

9 THE ROLE OF SCHOOLS IN MANAGING ALLERGIC DISEASES

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Allergy is a systemic condition that can cause a variety of disorders, such as asthma, rhinoconjunctivitis, dermatitis, urticaria and angioedema, digestive symptoms or anaphylaxis. The prevalence of allergic disorders is around 25% in schoolchildren in developed countries, and there is a rising prevalence in developing countries (Figure 1). Allergic children must face not only the same challenges in the school as their non-allergic peers but also added problems due to avoidance of triggers, their symptoms or to the treatment used for these.

Exacerbations of asthma or atopic dermatitis, and sleep disturbances associated to them or to rhinitis lead to increased absenteeism. The sedating effects of drugs such as antihistamines or the lack of adequate night sleep repair can cause presenteeism, a state in which the child attends school, but is not able to focus and assimilate the learning objectives, causing a worse school performance. Allergic children may seem "different" due to allergy signs, need to avoid allergy triggers or symptoms and thus become the target of teasing, bullying or isolation by peers, and teachers sometimes exclude aller-

KEY MESSAGES

- Allergy affects around 25% of schoolchildren, most of them fortunately with mild symptoms
- Non severe cases can nevertheless have impaired school performance and quality of life
- Severe, potentially fatal, reactions can occur at school, especially in food allergic children
- Education of all school personnel on identification and prompt treatment of severe reactions is needed
- A safer school will be obtained through a collaborative network involving physicians, nurses, school personnel, and patients' associations under the umbrella of an adequate legislation

Figure 1 One out of every four schoolchildren has an allergy. Which one is the allergic child in the photograph? A goal for the schools is to obtain a safe and friendly environment fully embracing the allergic child.

RCPCH Royal College of Paediatrics and Child Health

Allergy Action Plan

bsaci improving allergy care

THIS CHILD HAS THE FOLLOWING ALLERGIES:

Name:

DOB:

Photo

Emergency contact details:

1) ☎

2) ☎

Child's Weight: Kg

Mild-moderate allergic reaction:

- Swollen lips, face or eyes
- Itchy / tingling mouth
- Hives or itchy skin rash
- Abdominal pain or vomiting
- Sudden change in behaviour

ACTION:

- Stay with the child, call for help if necessary
- Give antihistamine:
- Contact parent/carer (if vomited, can repeat dose)

Watch for signs of ANAPHYLAXIS
(life-threatening allergic reaction):

AIRWAY: Persistent cough, hoarse voice, difficulty swallowing, swollen tongue

BREATHING: Difficult or noisy breathing, wheeze or persistent cough

CONSCIOUSNESS: Persistent dizziness / pale or floppy suddenly sleepy, collapse, unconscious

If ANY ONE of these signs are present:

1. **Lie child flat.** If breathing is difficult, allow to sit
2. **Give EpiPen® or EpiPen® Junior**
3. **Dial 999 for an ambulance*** and say ANAPHYLAXIS ("ANA-FIL-AX-IS")

If in doubt, give EpiPen®

After giving Epipen:

1. Stay with child, contact parent/carer
2. Commence CPR if there are no signs of life
3. If no improvement **after 5 minutes, give a further EpiPen®** or alternative adrenaline autoinjector device, if available

*You can dial 999 from any phone, even if there is no credit left on a mobile. Medical observation in hospital is recommended after anaphylaxis.

How to give EpiPen®

Keep your EpiPen device(s) at room temperature, do not refrigerate.
For more information and to register for a free reminder alert service, go to www.epipen.co.uk

Produced in conjunction with:

Allergy UK leading the fight against allergy

Anaphylaxis Campaign

www.bsaci.org Approved Oct 2013

Additional instructions:
If wheezy, give 10 puffs salbutamol (blue inhaler) via spacer and dial 999

This is a medical document that can only be completed by the patient's treating health professional and cannot be altered without their permission.

This plan has been prepared by: _____

Hospital/Clinic:

☎ Date:

Figure 2 Example of a written personal plan with identification of the child, description of potential symptoms, and steps on how to proceed if these appear. (Accessed at www.bsaci.org/about/download-paediatric-allergy-action-plans?EID=26293538&CID=4928446.)

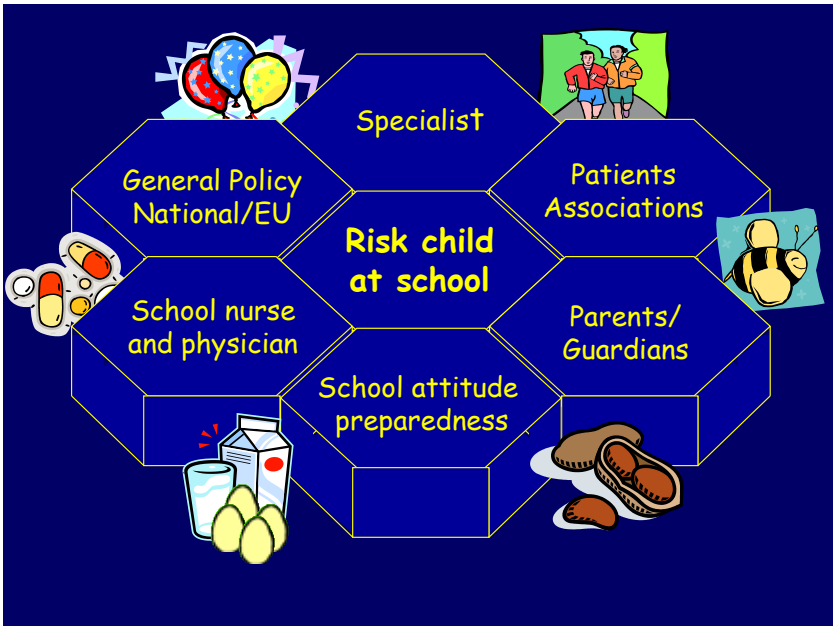

Figure 3 A safe school environment for allergic children requires the joint action of all stakeholders, with specific roles that include raising awareness, education, prevention, treatment and legislation.

gic children from certain activities for fear of a possible reaction.

The most worrying problem for children with severe allergy is "life-threatening reactions", as is the case for those with severe food allergy or severe asthma. For children with food allergy data from registers of anaphylaxis report severe reactions, including death, occurring at school. Similarly, there are reports of death or life-threatening symptoms from asthma in school premises or during school activities.

Recommendations have thus been made to obtain a safer environment at schools. It is advocated that every child with a severe allergy is provided a written personal plan with instructions on how to act in the case of presenting a reaction (Figure 2). An important pillar is the education of all school personnel (teachers, personnel working in canteens or playgrounds) regarding the prevention, recognition and prompt treatment of severe allergic reactions. The preventive measures must be implemented also in school outings, sports, and leisure activities.

To achieve this goal, the collaboration between all stakeholders is warranted: healthcare professionals including school physicians and nurses, school personnel, parents and families and associations of patients, all of them having an equal important role (Figure 3). There is an unmet need for legislative changes to define the rights of the allergic children and also the duties and the protection of school personnel when acting according to instructions provided by medical professionals.

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10 COMPREHENSIVE ALLERGY MANAGEMENT PLAN. TOWARDS A PATIENT-CENTERED ATTITUDE

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KEY MESSAGES

- Most patient organizations work on the assumption that allergy sufferers are self-empowering and take responsibility for themselves
- Allergy sufferers and their families should have access to relevant, up-to-date and sound knowledge at the time and in the complexity, depth and form they need
- Patients shall have the skills, life circumstances and support they need to live their lives as symptom-free as possible and with a consistently high quality of life
- Personalized measures are key for successful prevention and therapy of allergies
- The ideal mixture of mass media communication (online and print) and individual advising on a one-to-one or one-to-few basis together with online-based self-monitoring tools and personalized website surfaces can support patient-centered measures against the allergy epidemic

ALLERGY PATIENT ORGANIZATIONS

Patient organizations are mostly non-profit organizations that represent centre of excellence in the allergy field from a patient perspective. They seek visible public presence for the sake of creating awareness and carry allergy-prevention, better patient care, quality of life-related messages to the population. Patient organizations are independent contact points for allergy sufferers and carers, but also for other interested groups such as the media, companies, training centres, politics, authorities and associations. The services they offer range from advising individuals and training courses, self help groups through to prevention projects and campaigns for the population at large. These offerings are often made possible by widespread national and international networks and close cooperations with leading experts and professional bodies in the relevant spheres.

AIMS

Patient organizations want allergy sufferers and their families to have access to relevant, up-to-date and sound knowledge at the time and in the complexity, depth and form they need it in their respective situation. Sufferers shall have the skills, life circumstances and support they need to live their lives as symptom-free as possible and with a consistently high quality of life. The stakeholders in society shall take on their share of responsibility for the health-related living conditions and quality of life of all humans.

SERVICES

To achieve these aims, patient organizations offer sufferers, carers and other groups very well established services:

- high-quality documentation, publications and information
- expert advice
- interdisciplinary training courses
- prevention and information campaigns on current topics

Therewith, organizations support the health and quality of life of allergy sufferers, their families and potential sufferers and promote preventive action by a wide diver-

Figure 1 a - Implementing a healthy lifestyle as part of primary prevention; b - Developing the necessary skills to cope with the allergic disease; c - Expert individual advising on a one-to-one basis.

sity of players. They campaign for high-quality, broadly accessible services: primary prevention with the focus on living conditions and lifestyle (Figure 1a); secondary prevention by improving skills (Figure 1b). Aided by modern quality development, they strive for best professional practice.

TOWARDS A PATIENT-CENTERED ATTITUDE

In a global perspective, the number of sufferers steadily increases. The diversity of known allergic diseases and allergens increases. At the same time, there is growing evidence that personalized measures are key for successful prevention and therapy of allergies. In parallel to this, it is increasingly difficult to raise funds for patient organization activities. Today, allergy patient organizations are heavily challenged by these facts. By choosing the ideal mixture of mass media communication (online and print) and individual advising on a one-to-one or one-to-few basis (Figure 1c), this challenge has to be and will be mastered efficiently. In addition, online-based self-monitoring tools and personalized website surfaces can support patient-centered measures against the allergy epidemic.

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11 SOCIAL MOBILIZATION FOR MANAGEMENT OF ALLERGIC DISEASES

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KEY MESSAGES

- Active collaboration between all national and international health workers including doctors, allied health, pharmacists, political and health authorities in addition to patient associations is needed to tackle the allergy epidemic
- Teachers and caregivers should be informed and trained in attitudes and behaviors to deal with allergy, both in prevention therapeutics, and should be actively involved in reducing exposure to tobacco smoke
- The undergraduate and postgraduate training of all healthcare professionals should improve their knowledge on allergic diseases
- Education, awareness and mobilization campaigns leaded by scientific societies will raise the standards for allergic diseases early diagnosis and efficient management

Allergic diseases are a real non-infectious epidemic of the last century. The incidence of these diseases increase continuously every year, affecting millions of human beings of all ages, from infancy to old age. Allergic diseases are chronic conditions that affect the quality of life of allergy sufferers physically, emotionally and socially (Table 1). Sometimes the disease manifests itself in an acute form (asthma attack or anaphylactic reactions), which can lead to death.

These diseases carry significant health costs in different ways: direct and indirect, tangible and intangible. To achieve prevention, diagnosis and proper treatment of allergic diseases, it is essential that there is an active collaboration between all national and international health workers including doctors, allied health, pharmacists, political and health authorities in addition to patient associations, who play an essential role.

A significant proportion of individuals with allergy are underdiagnosed, undertreated, and dissatisfied with their treatment. Addressing these shortcomings may help us to optimize allergy care and ultimately the patient's quality of life.

There is still a general lack of knowledge about major allergic diseases. Undoubtedly, there are clearly some aspects that can be improved, as described in table 2.

In nurseries, colleges and universities around the world billions of children and young people are educated. Many of these students are suffering from allergic diseases. Teachers and caregivers should be informed and trained in attitudes and behaviors to deal with allergy, both in prevention (e.g. food allergies), and in therapeutics (e.g. asthma attacks induced by exercise). The consumption of tobacco products is still a major, unresolved problem in health education.

The training of all healthcare professionals should improve their knowledge on allergic diseases. Very few medical or nursing schools have Allergology as an undergraduate subject. Currently, there has been increased participation of teachers in considering Allergology as a relevant subject in the university. Similarly, it is very important to ensure that the specialty of Allergy is recognized in all countries within the postgraduate specialist training. GPs and pedia-

TABLE 1

Percentage of Patients (n=6236)[a] Experiencing Restrictions on Daily Life as a Result of Their Allergy						
	None of the Time	A Little of the Time	Some of the Time	Most of the Time	All the Time	Don't Know/ No Answer
Patients suffer from[b]						
Poor concentration	53%	21%	17%	6%	2%	0%
Tiredness	36%	22%	23%	12%	6%	0%
Trouble sleeping through the night	47%	20%	20%	9%	4%	0%
	Not at All Restricted	A Little Restricted	Somewhat Restricted	Very Restricted	Extremely Restricted	Not Relevant
Restrictions in[c]						
Carrying heavy loads	51%	19%	13%	6%	3%	8%
Exercising	29%	24%	18%	9%	4%	15%
Gardening	32%	15%	13%	9%	7%	24%
Housework	54%	20%	11%	5%	2%	8%
Running up stairs	42%	21%	14%	8%	4%	11%
Spending time outdoors or in countryside	36%	21%	17%	12%	9%	5%
Visiting friends and relatives		62%	19%	11%	4%	2% 2%
Playing with children	56%	15%	7%	3%	1%	18%
	Disagree Completely	Disagree	Agree	Agree Completely	Not Relevant	Don't Know/ No Answer
Agreement with the following[d]						
Feel ill	38%	39%	17%	3%	3%	0%
Sometimes feel frustrated or angry because of the condition	29%	28%	31%	9%	3%	0%
Sometimes feel embarrassed about symptoms (runny nose, watery eyes)	31%	30%	27%	8%	4%	0%
Sometimes do not feel very attractive because of the condition	29%	28%	30%	9%	4%	0%
Convinced people are bothered by the attacks	36%	40%	13%	3%	8%	0%
Condition has negative impact on sex life	41%	36%	11%	2%	10%	0%
Condition affects ability to exercise	23%	31%	29%	7%	10%	0%
Condition makes it hard to be spontaneous	36%	38%	18%	3%	5%	0%
Do not mind taking medication when around other people	7%	12%	39%	25%	17%	0%

[a] Patients completing the second self-reporting questionnaire. [b] Question: Thinking about the last time you suffered from allergy, how much of the time did you experience the following symptoms? [c] Question: Please indicate for each of the activities listed below how restricted you felt by your allergy the last time you experienced symptoms. [d] Question: Please indicate for each of the statements below to what extent you agree or disagree. Reproduced with permission from Chivato T, Valovirta E, Dahl R,et al. Allergy, living and learning: diagnosis and treatment of allergic respiratory diseases in Europe. J Investig Allergol Clin Immunol. 2012;22:168-79.

TABLE 2

Key steps in improving management of allergic diseases
• Improved undergraduate and postgraduate training (including related specialities such as primary care, pediatrics, pneumology, ENT, dermatology) in allergology and clinical immunology
• Education, awareness and mobilization campaigns organized by the leading scientific societies in the field
• Joining forces into International Alliances such as iCAAL and GARD. Involvement of competent authorities from the World Health Organisation to Ministry of Health in different countries

tricians should be trained properly in order to perform early diagnosis and correct long-term management of allergic diseases.

Although conventional mass media (TV, radio, press) and the Internet pay increasingly more attention to allergic diseases, it is still the responsibility of all stakeholders to ensure that adequate information is available to all patients, families and caregivers.

Scientific societies are leading several education, awareness and mobilization campaigns. An example of such kinds of initiative campaigns are the immunotherapy, food allergy and allergy awareness carried out by the EAACI.

Being allergic diseases a major problem, awareness initiatives should be treated with equal importance. For example, Global Alliance for Respiratory Diseases (GARD) activities are very important as they pursue awareness through different competent authorities from the World Health Organisation and Ministry of Health of countries.

Only by working together, can we make allergy and allergic diseases better known and in this way allergic patients will receive the best care they deserve.

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12 BEST BUYS FOR ALLERGY PREVENTION AND CONTROL

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KEY MESSAGES

- In children, the health is best served by giving similar recommendations to every child, that is a balanced diet, physical activity and a close connection with the natural environment, whether he/she is allergic or not
- Anti-smoking advice and legislation stopping smoking should be implemented since exposure to environmental tobacco smoke is still a major problem. Indoor and ambient air pollution should be tackled accordingly
- Modern, urbanized populations have lost factors balancing immune tolerance. The challenge is to gain the balance again and strengthen immune tolerance. The population should be encouraged to adopt sensible behaviors, getting rid of unnecessary diets, and consume diets that promote general health and immune balance
- Allergy should be addressed at a societal level: all healthcare providers, caregivers, kindergardens and schools personnel need to be provided with straightforward instructions to take care of allergic patients with mild symptoms

Strategies and recommendations for prevention of allergies have typically been quite restrictive based on relatively poor scientific evidence. New data imply that most children do not benefit in longer-term from avoidance diets or by taking extra precautions to avoid environmental allergen exposure. In clinical practice, the avoidance of inhalant allergens like pollens, animal danders or mites is difficult, if not impossible. For example, mite allergens can be reduced in homes, but they cannot be eradicated, and avoidance strategies to control mite allergies have been disappointing.

In children, the health is best served by giving similar recommendations to every child, that is a balanced diet, physical activity and a close connection with the natural environment, whether he/she is allergic or not. This does not mean that the environment should not be improved in many ways. Anti-smoking advice and legislation stopping smoking should be implemented since exposure of children to environmental tobacco smoke is still a major problem. Indoor and ambient air pollution should be tackled accordingly. Likewise, avoidance of potentially severe symptom-causing agents is still, and should stay, in the armamentarium of a competent allergist.

It is becoming apparent, however, that modern, urbanized populations have lost factors balancing immune tolerance. Population growth, rapid urbanization, destruction of natural (green) areas, deforestation, and changes in nutrition and household water all contribute to reduced biodiversity. This may reduce interaction between environmental and human microbiota, and immune dysfunction, impaired tolerance, and clinical disease may follow (Figure 1). The challenge is to gain the balance again and strengthen immune tolerance. A paradigm shift is taking place and affects especially prevention and practical guidance and education of patients. Everything people eat, drink, touch or breathe modulates their skin, gut and airway microbi-

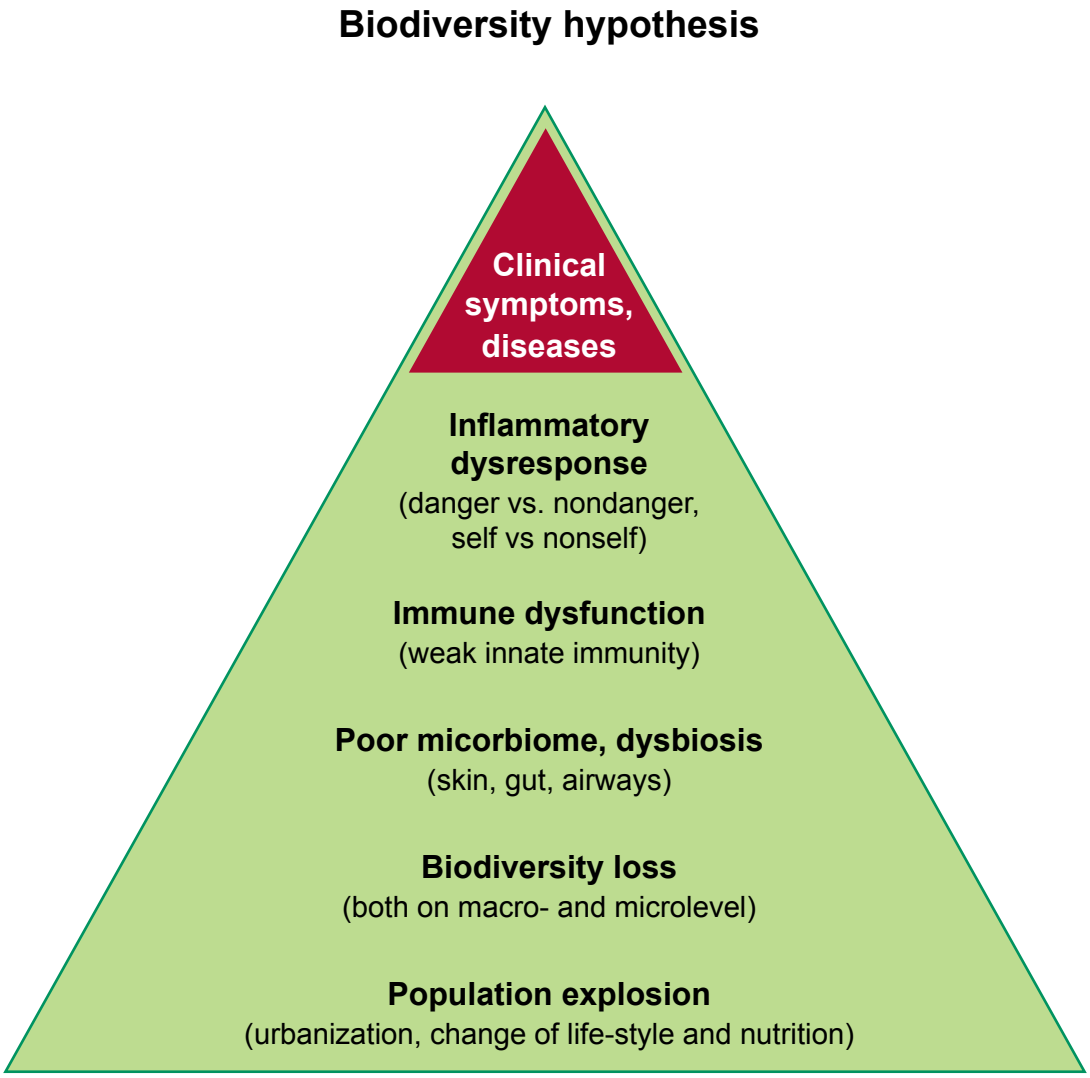

Figure 1 Population explosion has caused major changes in the interaction of humans with environment. Biodiversity loss both at macro- and micro-level is a major threat to humankind.

ome and keeps immune processes alert. Tolerance is an active process, trained and tested by the environment on line.

The numbers of allergic individuals are so high that not all of them can receive specialist medical care. It is neither in society´s nor the patients' interests to provide specialist treatment to large numbers of people with mild symptoms that can hardly be diagnosed as a disease. In the praxis of allergy prevention and treatment over treatment is not uncommon. General practitioners and nurses in primary care, in health care centers, well-baby clinics, and schools need to be provided with straightforward instructions to take care of patients with mild symptoms. The population should be encouraged to adopt sensible behaviors, getting rid of unnecessary diets, and consume diets that promote general health and immune balance.

The Finnish recommendations, along with the National Allergy Programme 2008-2018, are listed as an example in Table 1. The messages have been well received both by health care professionals and allergic patients. The first experiences of the new mode are encouraging.

TABLE 1

Practical advice to build-up and improve tolerance
Primary prevention
• Support breastfeeding, solid foods from 4–6 months. • Do not avoid environmental exposure unnecessarily (e.g. foods, pets). • Strengthen immunity by increasing connection to natural environments. • Strengthen immunity by regular physical exercise. • Strengthen immunity by healthy diet (e.g. traditional Mediterranean or Baltic type). • Use antibiotics only for true need, majority of microbes build-up healthy immune function. • Probiotic bacteria in fermented food or other preparations may strengthen immune function. • Do not smoke (e.g. smoking parents increase asthma risk in children).
Secondary and tertiary prevention
• Regular physical exercise is anti-inflammatory. • Healthy diet is anti-inflammatory, (e.g. traditional Mediterranean or Baltic diet improves asthma control). • Probiotic bacteria in fermented food or other preparations may be anti-inflammatory. • Allergen specific immunotherapy: ▪ allergens as is (foods) ▪ sublingual tablets or drops (pollens, mites) ▪ subcutaneous injections (e.g. insect stings) • Control early respiratory/skin inflammation with anti-inflammatory medication. • Find treatment for long-term control. • Do not smoke (e.g. asthma and allergy drugs do not have full effects in smokers).

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13 DEALING WITH THE IMPLEMENTATION GAP FOR ALLERGY PREVENTION AND CONTROL

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Allergic diseases are an epidemic in the modern society; therefore, there is an urgent need to counteract their increase. As in other non-communicable chronic diseases, strategies on prevention and control are being developed, focusing on promoting healthy lifestyles and early diagnosis and treatment. Nevertheless, implementation of these strategies remains a challenge.

Barriers to implementation of prevention and control programmes seem to be similar for many diseases (Figure 1). Therefore, in order to improve dissemination and subsequent application, these should comply, among others, with the following characteristics:

- Identification of risk factors and possible intervention measures
- Identify target populations
- Clear and simple objectives
- Realistic aims
- Design positive communication messages
- Measurable changes in appropriate indicators
- Involvement of all affected stakeholders (patients, society, healthcare system, health care professionals)
- Manageable costs
- Positive reinforcement through communication of achievements
- Use of highly accepted communication channels (TV, internet, smartphones, social media)

KEY MESSAGES

- Implementation of any disease prevention or control programme always represents a great challenge
- Planning clear and simple objectives is crucial for success
- Involvement of all stakeholders is a good strategy
- Using innovative and successful communication tools to reach the target populations will help with the implementation

As examples of such strategies, there are two programmes which have been developed, are implemented and are achieving remarkable success. In the field of allergy, the Finnish Allergy Programme 2008-2018, lead by Dr. Tari Haatela, is achieving a reduction of the allergy burden with relatively simple means. This 10-year implementation programme is aimed to reduce burden of allergies both at the individual and societal levels (Figure 2). This is done by increasing both immunological and psychological tolerance and changing attitudes to support health instead of over treatment of common and mild allergy symptoms. Severe forms of allergy are in special focus, e.g. asthma attacks are prevented proactively by improving disease control with the help of guided self-management.

The second example is in the area of cardiovascular disease. Research has proven that lifelong-acquired behavior is unlikely to change, and therefore acquisition of healthy behaviors should begin as early in life as possible. A series of initiatives are being implemented under the lead of the renowned cardiologist and researcher, Dr Valentin Fuster. An example of innovative tools to reach the target audience is the use a school-based program aiming at promoting health through a multilevel intervention supported by Sesame Street materials and educational background.

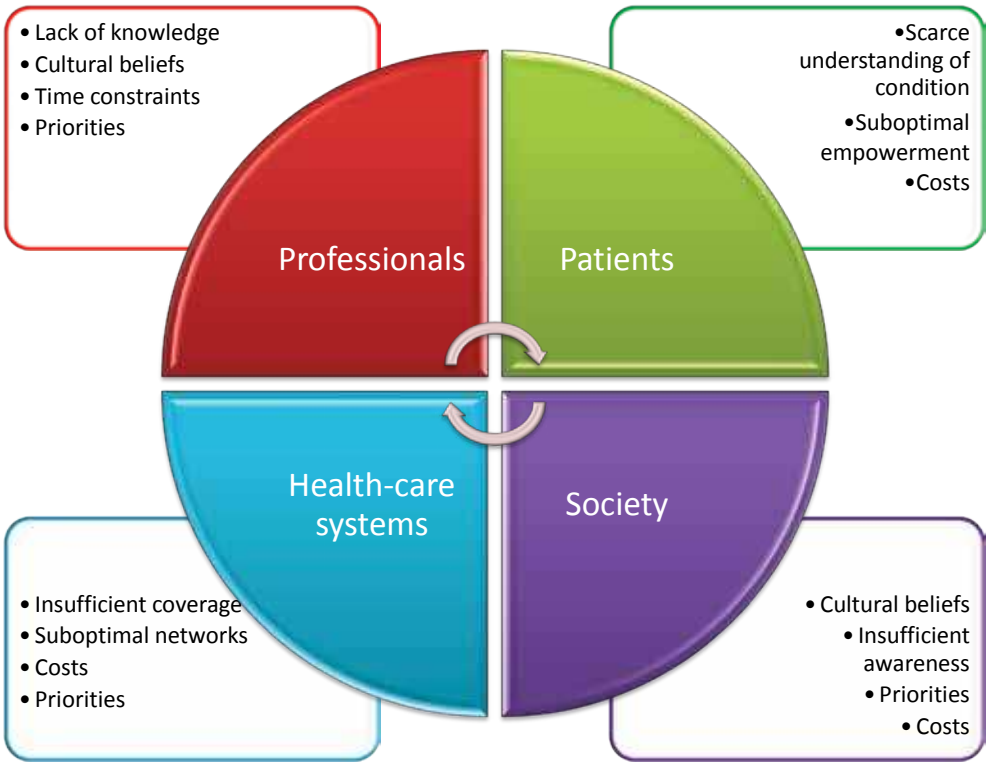

Figure 1 Potential barriers for the implementation of disease prevention and control programmes.

Figure 2 The key messages of the Finnish Allergy Programme 2008-2018. (*Reproduced with permission from Haahtela T, Valovirta E, Kauppi P, et al; Finnish Allergy Programme Group. The Finnish Allergy Programme 2008-2018 - scientific rationale and practical implementation. Asia Pac Allergy.2012;2:275-279.*)

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14 GENERATING RESOURCES FOR ALLERGY PREVENTION AND CONTROL

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KEY MESSAGES

- Several measures have been advocated for primary, secondary and tertiary prevention of allergic diseases
- More funding for research for allergy prevention is needed
- Support from policy makers for all levels of allergy prevention is warranted
- Systematic health community plans will improve health care at all levels for secondary and tertiary prevention of allergic disease

The worldwide increase in allergic sensitisation and allergic diseases in recent decades may represent a prize we pay for improved living-conditions, higher educational levels and modernised life style. Removing man from soil may illustrate how human defence towards environment shifted from protection towards harmful microbes to non-tolerance of harmless proteins. Our immune system must learn to live with new environments including reduced contact with microbial diversity, increased exposures to xenobiotics and other harmful environmental products, sedentary life styles and altered and altered diets, or we must take steps to change our modern life style. Reduced epithelial barriers, identified in asthma and atopic eczema, may enhance penetration of untoward environmental agents to an un-balanced immune system.

Primary prevention aims to prevent allergic sensitisation and allergic disease, secondary prevention to prevent further allergic diseases developing. Tertiary prevention targets the person with allergic disease to obtain optimal disease control and reduce risk of disease deterioration.

Recent decades have shown that development of allergic diseases starts early in life, even around conception or in pregnancy, and continue throughout life, exemplified by the direct association between tobacco smoke exposure and disease, and by the demonstration of methylation and histone modification of gene expression by exposure to tobacco products. The role of nutritional factors in disease development, such as vitamin D and anti-oxidants is unclear.

Epidemiological evidence suggest that delayed food introduction in infancy may promote allergy rather than tolerance. Thus, early oral introduction of food proteins in infancy may provide a natural primary preventing strategy, although documentation of such a strategy is warranted. The use of microbial products in pregnancy or infancy for primary or secondary prevention of allergy is suggested, but efficacy not proven.

Tertiary prevention by immune tolerance induction is well documented for pollen and insect venom allergy through allergen immunotherapy. Oral immune tolerance appears promising to food allergens.

Preventing maternal smoking in pregnancy can reduce asthma incidence through several mechanisms, including epigenetic effects by DNA-methylation. This includes reduced smoking among adolescents and women in childbearing age, including use of smoke-free tobacco (snus and e-cigarettes).

TABLE 1

Increased knowledge for primary and secondary prevention can be generated through research on
1. Mechanisms of allergy development
2. Tolerance induction and immune regulation after the instauration of allergic sensitisation
3. Barrier defects in skin and the respiratory tract
4. Human microbiota of different organ systems
5. Early introduction of food allergens
6. The link between atopic eczema and inhalant allergy

TABLE 2

Preventive strategies for combating allergy
• *Remove or reduce early exposure to pollutants*, including tobacco products and particulate air pollution
• *Strengthen research on allergy development and progression.*
• *Tolerance induction* by early natural allergen exposure, immune therapy and natural exposure to microbial diversity
• *Early, correct diagnosis and treatment* to obtain disease control and enable healthy living.

TABLE 3

Resources required for allergy prevention and control
• *Creation of systematic health community plans* to improve health care at all levels for secondary and tertiary prevention of allergic disease.
• *Support* from policy makers for all preventive levels: reducing environmental exposures, funding research, ensuring natural habitats and encourage individuals to improve life style and avoid smoking exposure.

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15 STRENGTHENING THE SPECIALITY OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY

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KEY MESSAGES

- The Allergy Specialty is recognised as a full specialty in 14 European countries and as a subspecialty in another 8 and there are countries, where is not recognized at all
- Given the increasing incidence of allergic diseases of epidemic proportions, it is time to raise the standards of care and to allow access to modern treatment options
- Allergy as a full well-recognized speciality, harmonised training and an uniform framework for managing allergic diseases is advocated
- Comprehensive Multidisciplinary Allergy Centers are recommended to coordinate optimal patient care and training of the health care professionals

Allergology or Allergology and Clinical Immunology is recognized as a full specialty in 13* countries (*In the Netherlands new specialists are trained as sub specialists in Internal medicine). It is a subspecialty in 8 other European countries. Some countries also recognize Pediatric Allergology as a full specialty or sub-specialty (Figure 1).

The spectrum of allergic diseases is broad and the number of causative agents is increasing. Often, allergens cause symptoms in different organs simultaneously or sequentially. Recently, several developments are challenging the role of healthcare providers in this discipline. First, there has been a steady increase in knowledge about the immunological processes that play a role in allergic diseases. No longer can allergic diseases be seen as solely IgE mediated, but rather are based on a complex and variable interaction between cellular and humoral factors within and outside the immune system. The increase in knowledge has lead to changes in diagnostic and therapeutic possibilities (e.g., new forms of immunotherapy, component resolved diagnosis) and it is expected that this tendency will continue. Second, the role of environmental exposure (allergens and irritants) and the impact of primary and secondary prevention (benefits and risks of allergen avoidance, infant feeding, application of pro/prebiotics, risk of tobacco smoke, role of epigenetics) are increasingly recognised as major players in the management of allergic diseases. Third, many epidemiological surveys have shown that the number of allergic patients in Europe and other developed and developing countries have increased dramatically, with one in three individuals being allergic. In addition, a notable proportion of individuals with respiratory allergy in Europe are underdiagnosed, undertreated, and dissatisfied with their treatment.

Considering all the challenges highlighted above it is time to raise the standards of care and allow access for the allergic patient to the most recent developments in allergy and clinical immunology science. The EAACI together with The European Union of Medical Specialists (UEMS) Section & Board on Allergology advocate a full Allergology specialty, formally recognised and structured.

In order to set the standards for knowledge the EAACI-UEMS examination on Allergology was initiated several years ago.

A further goal is to harmonise the training of Allergists in Europe. In

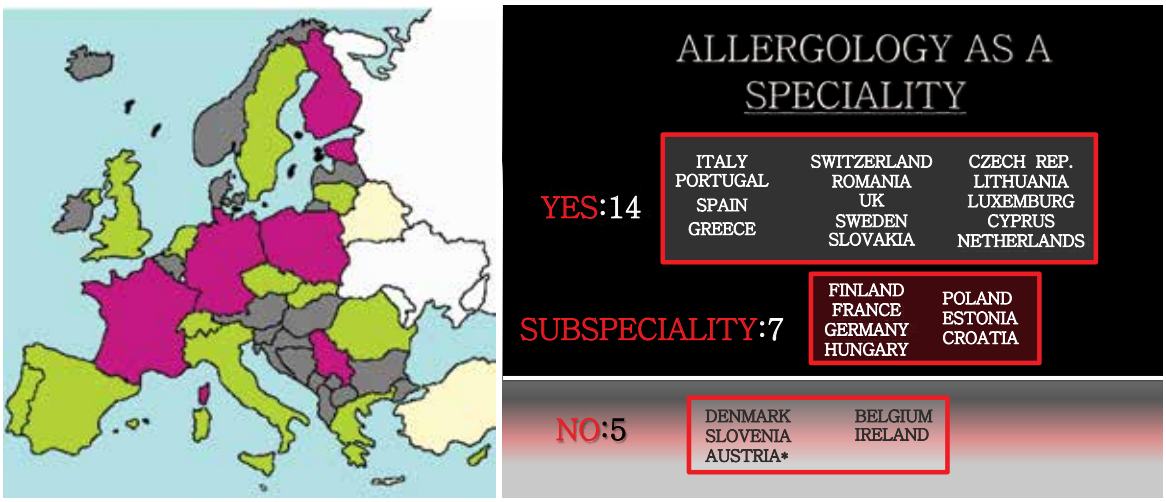

Figure 1 Left: Map of Europe showing countries with a full speciality (green) and a sub-speciality (red) of Allergology. Right: Table detailing individual countries.

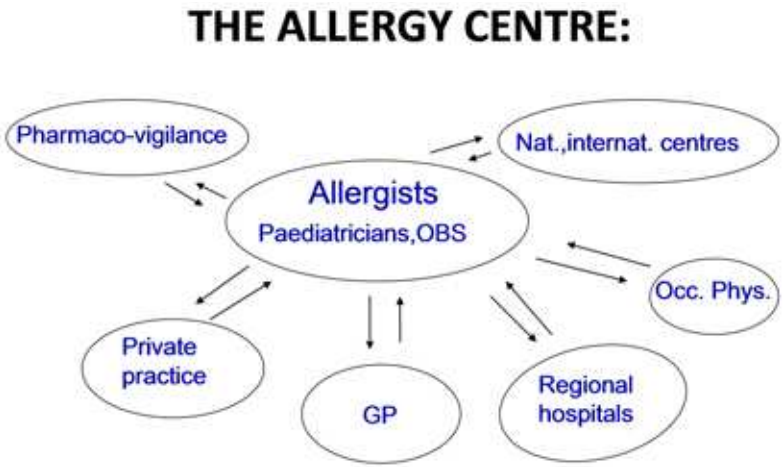

Figure 2 The network within and around the Allergy Centre. A close collaboration between allergists working in the centre and in private practice, other medical specialists and general practitioners is advocated. Moreover the centre allows easy access to pharmaco-vigilance and international centres and is ideally situated for training and research. (GP = General practitioners, OBS = Organ Based Specialists eg. dermatologists, Occ. Phys. = Occupational Physicians)

order to achieve this, international visitations of training centres are being held by the UEMS Section & Board Allergology. Moreover standards for training have been set by the Core curriculum and Logbook on Allergology.

Not only allergists, but also general practioners and other medical specialists take care of allergic patients. In order to achieve a rational distribution of tasks and responsibilities of different care givers, recently 'The Blueprint on Allergology' was published in the journal Allergy. In this publication comprehensive Allergy Centers (Figure 2) are recommended to coordinate patient care, allergy and clinical immunology research and training activities. The Allergy Centre aims at optimizing efficiency and increase quality at all levels.

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16 EAACI-UEMS EXAM IN ALLERGOLOGY/CLINICAL IMMUNOLOGY

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KEY MESSAGES

- The EAACI/UEMS Exam is a tool to improve, enhance and check knowledge in Allergology and Clinical Immunology offered annually since 2008
- The Exam comprises about 120 questions, revised annually from a question pool prepared by EAACI Task Force members and major European centres and is evaluated by professional institution (Institute for Medical Teaching, Bern)
- All candidates receive a detailed summary of their tests and, if successful, a valued EACCI/UEMS certificate. The Exam does not replace or substitute currently existing national examinations regularly held by national bodies

HISTORICAL BACKGROUND

The idea of an EAACI examination in Allergy and Clinical Immunology goes back to some discussion in the excom-committee during 2006 and 2007. 'The new Executive Committee (ExCom) members Werner Pichler from Bern, Switzerland and Gabriele Pauli from Strassbourg, France, proposed the idea of an common European Exam, and in particular some young ExCom members supported this "dream". On the other side, the idea of an EAACI exam encountered some skepticism, since allergy is handled quite differently by the various national societies, the rules to become an allergist/clinical immunologists differed quite widely and fear arose that by passing an European examination national regulations might be bypassed. After some internal discussion in the EAACI ExCom, and a positive outcome of the discussions with the UEMS in Göteborg in June 2007, where Jan de Monchy and Sergio del Giacco pushed the idea, both societies decided to work on an EAACI-UEMS examination. Both EAACI and the allergy/clinical immunology section at UEMS had already published some common guidelines and a list of topics relevant for the training in allergy and clinical immunology were already available both at national and international levels.

The examination was conceived as a knowledge examination based on multiple choice questions. The topics should cover Allergy (70 %) and Immunology (30 %), the later including also some aspects of Basic Immunology. The decisive step for a successful examination was the recruitment of a specialised, professional institution (Institute for Medical Teaching, IML, Bern), which was specializing in creating and formulating exam questions and was already involved in other European examinations. Werner J Pichler and Gabriele Pauli coordinated the first steps, created and collected questions (which turned out to be the biggest task) and adapted them for the Exam format.

EAACI and UEMS coordinated their efforts and in 2007 published their intention to organise an EAACI exam. The purpose of the exam was clarified (table 1). It was emphasized that passing this EAACI-UEMS examination was no license to practice in a country and this solved partly some concerns raised by National accreditation boards.

After creating and collecting almost 500 questions and careful selection of 100 questions for the

TABLE 1

Purpose of the EAACI-UEMS Knowledge Exam
• to booster the standards of Allergology/clinical Immunology in Europe;
• to enhance the harmonization of the allergy training in Europe;
• to provide an ability to compare oneself with the standard knowledge required from an allergologists in Europe,
• in the future to provide help in the organization of national examinations (e.g. written examination on a European basis, oral examination on a national basis.

Figure 1 1st EAACI-UEMS Knowledge Exam was organized in 2008 in Barcelona.

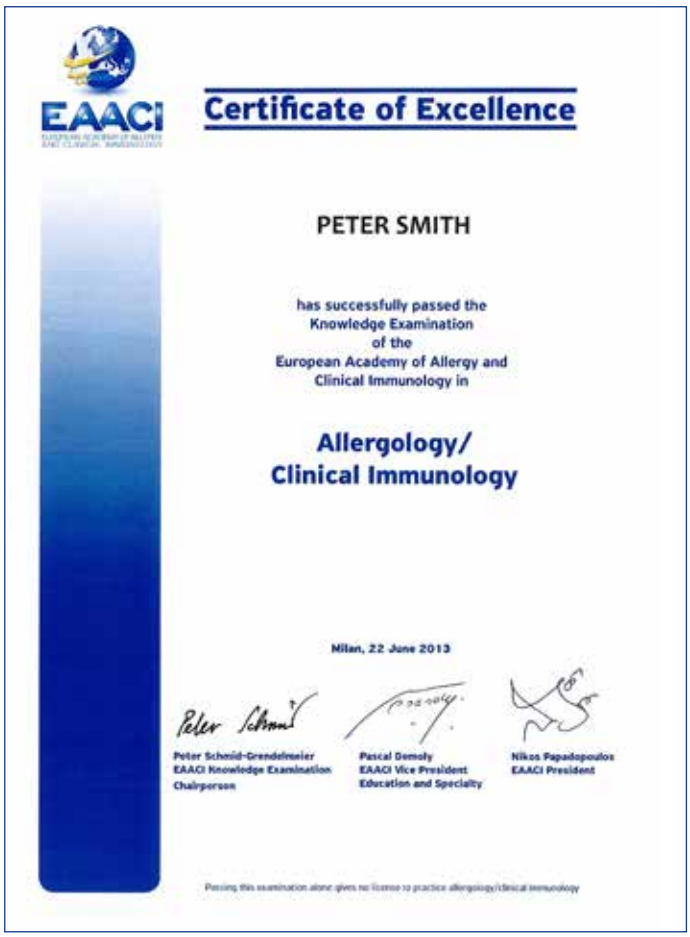

Figure 1 The EAACI-UEMS Certificate of Excellence.

exam, the first EAACI/UEMS examination took place in Barcelona in 2008 (figure 1). It was well organized and the participants came from more then 20 states, even from outside Europe. The questions were felt to be fair and 39 of 41 participants passed.

After 2009 Peter Schmid-Grendelmeier was elected as responsible for the examination. This choice guaranteed some continuity, as he was familiar with the IML, being a candidate y himself in 2008. Moreover, the value of the examination has been approved by some national societies, which combined a local, oral examination with the EAACI-UEMS knowledge examination.

THE PRESENT AND FUTURE

Since 2010, each year 30-50 participants took the examination. A further scope of the examination, to unify allergy teaching and standards in Europe, has also been approached. Regularly candidates come also from overseas such as Middle East, but also farer Asia, Africa or Latin America are participating as it offers a good opportunity to enhance and check the personal knowledge in allergy and clinical immunology.

More than 200 candidates, members of many National Societies, have already successfully passed the examination. The acceptance of this well structured and validated exam is rapidly increasing and it counts in an increasing number of nations as a sign of excellent knowledge in the field of allergy and clinical immunology.

The examination comprises questions, revised annually from a question pool, and many new questions are prepared by EAACI Task Force members and major European centres. They are carefully evaluated by the EAACI Exam/Knowledge Test Committee and also the IML and are continuously adapted to modern exam standard and techniques. A blueprint with relevant literature is available on the EAACI website. The 180-minute exam contains about 120 multiple-choice questions, currently all in English. Language dictionaries are permitted, and translations into other major languages foreseen. UEMS is strongly supporting the Exam, by promoting and collaborating in the Exam TF. Both EAACI and recently also UEMS are offering financial support to enable on request reduced exam fees for candidates from low income areas.

All candidates receive a detailed summary of their tests and, if successful, a valued EACCI/UEMS certificate (figure 2). The Knowledge Test in Allergology/Clinical Immunology does not replace or substitute currently existing national examinations regularly held by national bodies. EAACI members have the opportunity to use this Knowledge Test as a very useful tool for self-evaluation.

EAACI and UEMS are now proud of their successful exam. Even the skeptics have been convinced of its value. It proves to be a big step forward to better allergy training in Europe.

17 MANAGING ALLERGIC DISEASES IN DEVELOPING COUNTRIES

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KEY MESSAGES

- The main difficulties in the management of allergic diseases in developing countries are caused by insufficient level of health care, heterogeneous inhabitation and lack of educational programs for healthcare providers and patients
- A marked heterogeneity in prevalence is observed between countries or between regions within one country, highly dependent on environmental and social factors
- Management of allergic diseases is based on the availability of essential drugs and their financial affordability

More than 100 countries with almost 85% population of the world are considered to be developing countries (DCs). The main difficulties in the management of allergic diseases in DCs are caused by insufficient level of health care, heterogeneous inhabitation and lack of educational programs for healthcare providers and patients. A marked heterogeneity in prevalence is observed (Table 1).

The prevalence of allergic diseases and their severity is highly dependent on environmental and social factors. Although it is hard to prove the association between high IgE levels and atopy in Africa because of wide-spread of parasitic infections, reported prevalence rates from the ISAAC study that included 22 centers from 16 African countries, varied for wheezing between 4–22 %, for allergic rhinoconjunctivitis between 7–27 %, and for eczema between 5–23 %. For some higher-income African urban centers, the rate of current wheezing was comparable to European countries, and reflected an increase over the past decade. In general, the spread of allergic diseases worldwide is positively associated with urbanization and the standards of living. One of the most interesting findings of the ISAAC study was the striking difference in asthma prevalence in populations with similar genetic backgrounds from different environments. The prevalence of asthma was two times higher in Hong Kong, the most developed and westernized Chinese city, compared to Guangzhou located approximately 200 km north-west. According to the ISAAC study the management of allergic diseases in DCs is based on the availability of essential drugs and their financial affordability. For example, chlorpheniramine and beclomethasone are part of the WHO essential drugs list, while allergen immunotherapy is listed as limited accessibility.

In Russian Federation and other Commonwealth of Independent States (CIS) countries the network of specialized allergy centers provides sufficient care for allergic patients. Allergy and Clinical Immunology is a separate speciality. For the assessment of the prevalence of allergic diseases in Russian Federation, standard international and European approaches are applied: ISAAC or ECRHS questionnaires, locally adopted questionnaires, skin tests, IgE measurement etc. Data on the prevalence of allergic diseases and allergens in Russian Federation is shown in Figures 1 and 2. The prevalence of allergic diseases is influenced by climatic and geographical features of the region (Figure 1 and 2). International (ARIA, GINA) and local guidelines are applied in the management

TABLE 1

Prevalence of allergic diseases in some developing countries

Country		Asthma	Allergic rhinitis	Eczema	Food Allergy	Authors
Vietnam, Hanoi (questionnaire)		5.6%				Hoàng Thị Lâm, Bo Lundbäck et al., 2011
Iran (questionnaire)		3.9% (CI; 3.2 to 4.7%)				Mohammadbeigi A, Hassanzadeh J, Mousavizadeh A., 2011
China (questionnaire) Children 6-12 years		3.3%	9.8%	5.5%		Li F, Zhou Y, Li S, Jiang F et al., 2011
Turkey (questionnaire)	Adults		29.6%,			Cingi C, Ozkiraz S. et al 2010
	Children 11.5±3.3 years	11.5%	22.1%	10.7%		
South Africa	Urban children	3.6%	17%			P.C. Potter, 2009
	Rural, children 6-7 years	0	0,8 – 14.9%			
	Children 13-14 years		1.4 – 39.7%			
Rwanda(questionnaire) in Kigali Adults		8.9%				Musafiri S, Brusselle G et al., 2011
Republic of Ghana					11%	Obeng BB, Yazdanbakhsh M, 2011
Zimbabwe	Rural children	0.1%				Keeley et al 1991
	Urban children	3.2%				
Brazil	Children 10-14 years	11%	33.2%			Toledo MF, Rozov T, Leone C, 2011
	Sao Paulo teenagers	6.8%	36.6 – 37.6%	16.2%		

of allergic diseases, and access to specialized care is fully accessible for the whole population.

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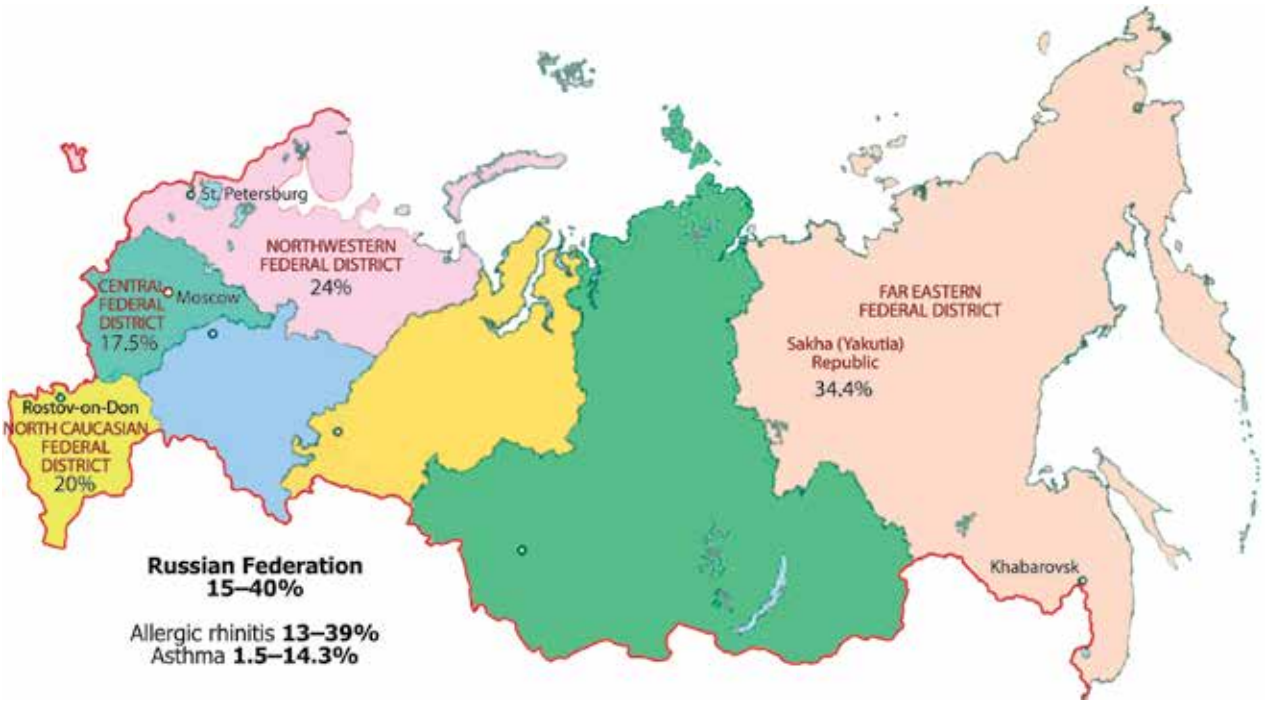

Figure 1 The incidence of allergic diseases in Russian Federation.

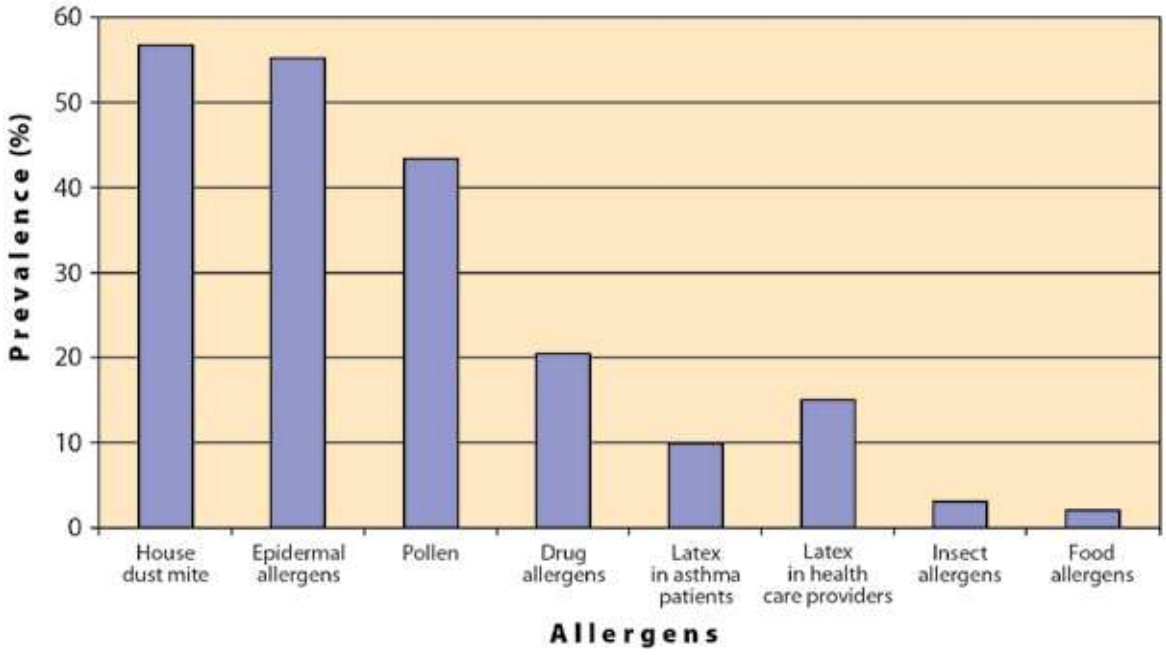

Figure 2 The most common allergens in Russian Federation.

18 THE "ONE HEALTH" CONCEPT AND ALLERGIC DISEASES

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KEY MESSAGES

- One Health frames the complex interactions between human, animal and environmental health
- One Health is a unique approach to cope with allergies
- One Health also includes food safety and security, agriculture, water, sanitation and hygiene
- One Health focuses on equity and is key for human sustainable development

DEFINITION OF ONE HEALTH IN THE CONTEXT OF ALLERGIES

Many emerging health issues are linked to increasing contact between humans and animals, the industrialization of food production, and environmental pollution. Urbanization, globalization, climate change, deforestation and other changes in land use, the creation and operation of large terrestrial and marine industrial food production units, and microbial and chemical pollution of land and water sources have created new threats to the health of both animals and humans. These complex interactions impacting human health need integrative approaches to cope with. A promising approach, briefly introduced here, is the "One Health" concept. One Health frames the complex interactions between human health, livestock, pet and wildlife health, ecosystems health, climate, agriculture, food systems, water and sanitation, and human development (Figure 1).

RECENT DEVELOPMENTS IN ONE HEALTH

Whereas the "One Health" approach for many years was limited to an interdisciplinary collaboration in human and veterinary medicine, with substantial added value in zoonoses control and related health service provision, One Health has evolved to a broad and holistic paradigm to include an ecological dimension, and most recently the economic and social dimension addressing equity, governance, justice, livelihood, and welfare. One Health, thus has begun to move beyond the status of a mere concept to become a truly global movement at the interface of science, society, policy and practice. This movement is deeply interdisciplinary and cross-sectorial and provides a fascinating, powerful framework that a variety of professional communities and social groups can adhere to (Figure 1).

The One Health paradigm will be helpful in reversing the worst of current problems at the human-animal-environment and development interface thus fostering a more sustainable way of life on our planet (Figure 2). Keeping in mind that more than half of the worldwide population is living in urban areas and rural exodus continues to grow, One Health may become a crucial approach to successfully cope with all the drivers and consequences in urbanization dynamics.

Mitigating the impacts from threats like emerging pathogens, toxicant releases, climate change, and changes in the built environment requires pooling of global public health resources and capabilities across multiple disciplines. By collaboration among multiple sectors such as veterinary medicine, human medicine, environment, wildlife, livestock, agriculture, water, sanitation and

Figure 1 The One Health paradigm at the human-animal-environment and development interface - a global movement at the coalescence of science, society, policy and practice, which is deeply interdisciplinary and cross-sectorial, and relates to an integrative health risk approach as an essential tool for an effective and efficient handling of health risks. (Ammann WJ, Colbert M, Rechkemmer A. One Health: Summary and Outlook, in Colbert M, Stiffler M, Ammann WJ (Eds.). GRF One Health Summit 2012 – One Health – One Planet – One Future: Risks and Opportunities, Extracts from the Proceedings, OECD- GRF Davos, p. 115 – 120).

ONE HEALTH
ONE PLANET ONE FUTURE

Figure 2 The logo of the annual GRF Davos One Health Summits expressing the global One Health movement, fostering a more sustainable way of life on our planet (http://onehealth.grforum.org/home/).

hygiene, food security and public health, One Health can substantially contribute to reduce existing and emerging global threats.

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19 ALLERGY AND ACTIVE AND HEALTHY AGEING

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KEY MESSAGES

- The concept of active and healthy ageing (AHA) is the process of optimizing opportunities for health to increase healthy life expectancy, healthy life years and quality of life for all people as they age
- Poor health is largely shaped by non-communicable diseases (NCDs) that share common risk and socio-economic factors, and cluster in co-morbidities
- Allergic diseases and asthma are the most common NCDs in children and have been on the rise in recent decades. They represent a major cause of health care and socioeconomical burden
- Early life events play a fundamental role in health and on NCD development. AHA should be promoted very early in life

The broad concept of active and healthy ageing (AHA) is the process of optimizing opportunities for health to increase healthy life expectancy, healthy life years and quality of life for all people as they age (http://www.who.int/ageing/active_ageing/en/index.html). AHA allows people to realize their potential for physical, social (economic, cultural, spiritual and civic affairs) and mental well being throughout the life course. The WHO report "Good Health adds to life years" (2012) approaches ageing from a life-course perspective and assumes that we age from the moment we are born (http://whqlibdoc.who.int/hq/2012/WHO_DCO_WHD_2012.2_eng.pdf).

AHA is a major societal challenge, common to all populations. Poor health is largely shaped by non-communicable diseases (NCDs), which share common risk and socio-economic factors, and cluster in co-morbidities. They are intertwined with ageing and represent a major cause of frailty. Early life events play a fundamental role in health and on NCD development. AHA should be promoted very early in life.

Allergic diseases and asthma, the most common NCDs in children, have been on the rise in recent decades. They represent a major cause of burden, school and work absenteeism. Children with asthma have a risk for COPD in adulthood. That is why the 2011 Polish Presidency has made the prevention, early diagnosis and treatment of chronic respiratory diseases in children a priority for the European Union's public health policy in order to reduce health inequalities across European societies. In its conclusions, the 3131st Council meeting of the EU invites member states to tackle the problems, which constitute the biggest risk factors that could trigger a chronic respiratory disease: tobacco smoke, poor indoor air quality and outdoor air pollution. Health education of children, parents and teachers is recognized as important in this regard, as well as training of health professionals.

Allergic diseases and asthma occur very early in life and often persist life-long. They impact physical, social (economic, cultural, spiritual and civic affairs) and mental well-being throughout the life course. Early diagnosis, prevention and management of chronic respiratory diseases in children will help people to cope with their disease, to have a normal life and to age well.

Figure 1 The concept of Good Health as promoted by the World Health Organisation.

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20 ALLERGY IN INTERNET

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KEY MESSAGES

- The Internet has become a significant source of health information and support for both patients and doctors
- Information on allergy in internet can be sometimes misleading, non evidence-based and potentially dangerous
- Therefore, it is fundamental that both patients and doctors refer to accredited institutions websites, such as those created and/or endorsed by international scientific societies
- Apart from educational material, internet can provide patients platforms in which they may share their experiences with other patients or doctors
- Doctors may use internet also to improve their career, through scientific societies and/or journals websites

The Internet has become a significant source of health information and support for patients with chronic conditions such as allergy, and their caregivers, including health care professionals. Among the countless websites regarding allergic diseases, we can distinguish sites with high quality content from sites with low evidence grade and questionable information. Therefore, it is important that both patients and doctors may count on few but trusted websites, which are certified by the world's most prestigious scientific societies.

TRUSTED WEBSITES FOR PATIENTS

Probably the most interesting and comprehensive websites containing reliable informations on allergies for patients, come from three of the most prestigious scientific societies in the field: EAACI (with it's "Patients area", see Figure 1 upper-left quarter), ACAAI (with the website called "Allergist", see Figure 1 upper-right quarter) and AAAAI (with the "Conditions and treatments" sub-section of its main website, see Figure 1 lower-left quarter) (see Box 1).

"EAACI Patients Area" provides a large and comprehensive amount of information for patients, ranging from the description of allergic diseases, their correct diagnostic work-up and treatment options, to information on how to interpret, in a evidence-based manner, complementary and alternative medicine approaches to allergy, and to providing easy access to useful tools for allergic patients (i.e.: information on travelling with allergies or pregnancy and allergy, the list of European and world wide patient associations, and a world-map of pollen counts). Both "EAACI Patients Area" and "Allergist" provide interesting interactive tools to let patients seek for symptoms or organ involvement to obtain information on possible allergic diseases which may explain their symptoms ("Think you have an allergy" and "Allergic and immunologic diseases & causes" for "EAACI Patiens Area", "The virtual allergist" for the AAAAI website). A similar tool is available also on WAO and ACAAI websites, but the latter is limited to nasal complaints ("My nasal journal"). An other website in which patients may find comprehensive information on a specific aspect of allergies, food allergy, is FARE (Food Allergy Research & Education).

One of the important patients' need is to share their doubts/opinion with expert doctors and with

Figure 1 Screenshots of homepages of principal patients-targeted websites endorsed by the most prestigious international scientific societies in allergy and clinical immunology.

BOX 1 – List of suggested internet resources for PATIENTS:

INTERNATIONAL SCIENTIFIC SOCIETIES FOR PATIENTS:

- **"Patients Area" - EAACI** (www.eaaci.org)
- **"Allergist"- ACAAI** (www.acaai.org/allergist)
- **"AAAAI – Conditions and treatments"** (www.aaaai.org/conditions-and-treatments.aspx)
- **"WAO – Patient resources"** (www.worldallergy.org/patient-resources)
- **"FARE – Food Allergy Research & Education"**: (www.foodallergy.org)

DISCUSSION BOARDS ON ALLERGY:

- **"AllergyUK forum"** (forum.allergyuk.org)
- **"AllergyChat"** (www.allergychat.org/allergy_forum)
- **"Health Boards – Allergy"** (www.healthboards.com/boards/allergies)

BOX 2 – Main internet resources for DOCTORS:

PRINCIPAL SCIENTIFIC ARTICLES DATABASES:

- **"PubMed"** (www.ncbi.nlm.nih.gov/pubmed)
- **"EMBASE"** (www.elsevier.com/online-tools/embase)
- **"Scopus"** (www.scopus.com)

ALLERGEN DATABASES:

- **"Allergome"** (www.allergome.org)
- **"SDAP - Structural Database of Allergenic Proteins"** (fermi.utmb.edu)
- **"Protall"** (www.ifr.ac.uk/protall/database.html)
- **"AllFam"** (www.meduniwien.ac.at/allergens/allfam)
- **"AllergenOnline"** (www.allergenonline.org)

CAREER/JOB OPPORTUNITIES FOR ALLERGISTS:

- **"EAACI – Job center"** (www.eaaci.org/resources/job-center.html)
- **"AAAAI - Career Connections Center"** (careers.aaaai.org/home)
- **"ACAAI – Job source"** (jobs.acaai.org)
- **"NEJM Career Center"** (www.nejmcareercenter.org)
- **"The Lancet Careers"** (jobs.thelancet.com)
- **"JAMA Career Center"** (jama.careers.adicio.com)

other patients; an "Ask the expert" section is present in most of the previously mentioned websites, while discussion boards between patients are present in other websites as "AllergyUK", "AllergyChat" or "HealthBoards". Even if these websites cover a patients' need, it is important to remind that they cannot be considered a reliable source of scientific/correct information on allergies. This is one of the reasons that led scientific societies as EAACI and AAAAI to publish their own Facebook pages in which evidence based information on allergy is spread to a larger audience.

TRUSTED WEBSITES FOR DOCTORS

Both experts in these field (specialists) and those who are in training (i.e.: residents) or more generalist doctors (i.e.: general practitioners) may need to seek for professional and scientific information on internet (see Box 2).

As far as scientific update, doctors may count on institutional and universally recognized database such as "PubMed", "EMBASE" or "Scopus" to seek scientific articles, or allergen database such as "Allergome", "SDAP", "Protall", "AllFam" or "AllergenOnline", or to a variety of allergy textbooks which are now available online.

Internet gives also the doctors the opportunity to easily improve their career through institutional websites collecting career/jobs opportunity in the field (i.e: a specific sections into both EAACI and AAAAI websites, or specific databases into more generalist websites such as those of some prestigious scientific journals like NEJM, The Lancet, JACI, Allergy or JAMA).

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21 iCAALL: INTERNATIONAL COLLABORATION IN ASTHMA, ALLERGY AND IMMUNOLOGY

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iCAALL Chairs

KEY MESSAGES

- In 2050 it is predicted that up 4 billion people in the world will suffer from asthma, allergic rhinitis and atopic dermatitis
- The burden of these prevalent allergic conditions, coupled with acquired and congenital immunodeficiencies and drug allergies, will negatively impact all communities and the overall world economy
- The American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; the European Academy of Allergy and Clinical Immunology; and the World Allergy Organization have formed a collaborative initiative termed the International Collaboration in Asthma, ALlergy and ImmunoLogy (iCAALL)
- The aim of iCAAL is to coordinate communication about allergies, asthma, and immunologic diseases and to raise general awareness on a global level
- International consensus statements (ICONs) were developed to serve as reference tools for physicians and other health care professionals and as educational tools for policymakers and the general public. The ICONs combine the best scientific evidence with international expert consensus and are adaptable to circumstances in all countries worldwide, allowing for modifications based on the availability of regional diagnostic and therapeutic interventions

The prevalence of Allergic Diseases and Asthma continues to increase worldwide. In 2050, the world's population will likely reach 9 to 10 billion, among which 2 to 4 billion will suffer from allergic diseases, including asthma, allergic rhinitis and atopic dermatitis. These conditions are compounded by a number of comorbidities. The burden of these prevalent, allergic conditions, coupled with acquired and congenital immunodeficiencies and drug allergies, will have a very strong adverse impact on all communities and will negatively affect the overall world economy.

To address these concerns and prepare for the resulting needs worldwide, the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; the European Academy of Allergy and Clinical Immunology; and the World Allergy Organization have formed a collaborative initiative termed the International Collaboration in Asthma, ALlergy and ImmunoLogy (iCAALL) (figures 1 and 2).

The mission of iCAALL is to enhance the coordinated communication of information about allergies, asthma, and immunologic diseases and to raise general awareness of these diseases on a global level. It will develop communication and education tools for specialists, general practitioners, and other health care professionals and, ultimately, provide global information for the general public, patients, and policymakers. Ideally, this collaboration will result in a greater awareness about allergies, rhinitis, asthma, and immunologic diseases, resulting in more effective care for patients and increased allocation of resources for research and patient

Figure 1 Four International Societies joined forces into a global alliance against the heavy burden of allergic and immunologic disease.

Figure 2 ICAALL Steering Committee 2011-2013 during the EAACI Annual Meeeting in Geneva June 2012. EAACI: Jan Lötvall, Cezmi A. Akdis, Nikolaos G. Papadopoulos, AAAAI: Dennis K. Ledford (iCAALL Chair), Thomas B. Casale, Wesley Burks, WAO: Richard F. Lockey, Ruby Pawankar, Lanny J. Rosenwasser: ACAAI: Dana V. Wallace, Stanley Fineman, Richard Weber.

care, thus benefitting affected patients and the greater population.

The first project underway is the development of international consensus statements (ICONs) to serve as useful resources for physicians and other health care professionals who treat patients with allergic and immunologic diseases. ICONs are also intended to educate policymakers about the importance of providing resource allocation to ensure optimal patient care and to sustain research. The ICONs combine the best scientific evidence with international expert consensus and are adaptable to circumstances in all countries worldwide, allowing for modifications based on the availability of regional diagnostic and therapeutic interventions.

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22 VISION AND ROADMAP TO FIGHT WITH ALLERGIES

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KEY MESSAGES

- Allergy epidemic affects more than one billion patients with a global rise in prevalence, which may reach up to 4 billion affected individuals in 2050
- The already existing many unmet needs and a huge socioeconomic burden to health care systems is expected to substantially increase
- Effective policies and strategy development are needed at the global, regional and national level
- Efforts to overcome unmet needs should focus on 4 main directions:
  - Intensive research and development
  - Improved patient care at the global level
  - Increased public awareness
  - Upgrade of the Allergy domain in the political agenda
- A "Global Allergy Fight Strategy" should be developed
  - All stakeholders should be involved
  - A multidisciplinary and scientific approach should be used
  - The "One Health" concept should be integrated
  - Next generation guidelines should be developed
  - World Allergy Centers and integrated surveillance network should be established
  - Existing know how from successful approaches in the past should be implemented and adapted to local conditions

With an epidemic rise during the last 60 years, today, allergic diseases are affecting the lives of more than one billion people worldwide, and their prevalence is expected to reach up to 4 billion in 2050. The prevalence of allergic diseases and socioeconomic impact are particularly on the rise in urbanizing regions and globalizing world in association with environmental and lifestyle changes. Apart from individual suffering of patients, allergic diseases present a very high socioeconomic burden to health care systems and families. In addition, patient care and access to diagnosis and treatment is inadequate in many developing regions and countries. Effective policies and strategy development are needed to fill this gap at the global, regional, national level (Table 1).

The **efforts** to overcome high numbers of unmet needs in allergic diseases are described in "section H" and can be grouped in three directions:

A) **Research and development** should be synergized and prioritized in order to achieve sustainable results on prevention, biomarkers, curative treatment, anti-viral vaccines, and novel drug development. There are a number of barriers and obstacles in grant giving bodies to be solved, particularly to support human immunology and allergy research (Table 2).

B) **Improved patient care at the global level** requires a world-wide approach to identify barriers for prevention and cure, develop patient registries and next generation guidelines, improve access to diagnosis and essential drugs in low income countries, implement full environment control, provide

TABLE 1

Efforts for increasing awareness in the political bodies for allergy and asthma
• Global Allergy and Asthma European Network (GA²LEN) was established with the efforts of EAACI in 2004 as an EU FP6 Network of Excellence. GA²LEN still continues as a non-profit network.
• Allergy was listed in the food and agriculture group in the EU research grants until 2007. EU accepted allergy as an important health problem in 2007 with the efforts of the EAACI and GA²LEN.
• Allergy is not included in Horizons 2020 programme. Many attempts and several one day awareness meetings have been organized in the European Parliament and attended by patient organizations, EAACI leadership and members of the Parliament in Brussels during the recent years, which were specifically intensified during the last year.
• ICAALL: The American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; the European Academy of Allergy and Clinical Immunology; and the World Allergy Organization have formed a collaborative initiative termed the International Collaboration in Asthma, ALlergy and ImmunoLogy (iCAALL) in 2011. 12 International Consensus "on" (ICON) papers have been planned and 7 have been published so far.
• The results of the Finnish Allergy and Asthma Programmes demonstrated that allergy and asthma burden can be substantially decreased by relatively undemanding methods doable by every country (Chapter H12). This strategy is slowly being adapted to local conditions and implemented by some national health-care systems

psychological help directly and routinely without any need for consultation and implement every aspect of education of patients, primary care physicians and allied health personnel.

C) **To increase the public awareness**, it is now essential to publicly position allergic diseases and asthma as one of the most important causes of chronic morbidity and health care burden. Allergy and asthma focused patient organizations should be immediately established in all countries. A significant number of international alliances, societies, networks and academies are working on this. Intensive efforts should be performed at the level of local governments, United Nations, WHO, EU etc.

A worldwide strategy to fight and manage allergic diseases should be developed (Table 3).

A) **All stakeholders** including specialists, primary care physicians, nurses, dieticians, psychologists, pharmacists, patient organizations, educators, industry, and policy makers should be involved. The roles of all stakeholders have been mentioned in detail in the previous chapters in section "H".

B) **The speciality of "Allergology"** should be strengthened as a full specialty and should be world wide harmonized.

C) **Modern global guidelines** should be developed and implemented for the management of allergic diseases, asthma and co-morbidities. The new generation guidelines should provide structured, multidisciplinary, region and environment-oriented and individual patient-focused solutions, with full considerations on differences across cultures.

D) There is substantial experience of already established strategies and associations. We should avoid reinventing the wheel and utilize and implement the existing know how. For example, one of the most valuable experiences in our fight with allergies is the success of the **Finnish Allergy and Asthma Programmes**. It is now fundamental to disseminate the Finnish experience to the whole world, collect feedback and further improve.

E) Global management of allergic diseases should be integrated

TABLE 2

Obstacles in research grants and grant giving bodies
• Lack of political awareness and low understanding and priority setting for the allergy epidemics
• Curative approaches and research for prevention has not been so far efficiently supported
• Small quantities of grants have been given to hypothesis-based research, although the real need is for large scale, non hypothesis based, in dept research, which is now possible with the novel developments in next generation DNA and RNA sequencing, exposome and epigenetic analysis and biomarkers
• Human research is receiving relatively less funding in many grant giving bodies compared to animal models
• Many major grant giving bodies had to decrease their budgets due to economical conditions in the US and Europe during the last years

TABLE 3

To do list for the global allergy fight strategy
• Accept allergies and asthma as a Global Public Health Problem
• Upgrade "Allergy" on the political agenda
• Perform research and develop strategies to reduce risk factors
• Appreciate the role of primary care, allied health personnel and pharmacists as the central link between patients and physicians and initiate global education programmes
• Develop intensive public education and awareness programmes
• Improve and disseminate the "Finnish Programmes"
• Increase research funds in general
• Prioritize prevention and curative treatments in research
• Generate resources for prevention and control
• Strengthen the specialty of "Allergology"
• Increase awareness on and implement the "One Health" concept
• Harmonize and economize the educational and awareness activities of main associations through ICAALL

with the "**One Health**" concept that acknowledges the systemic interconnections of human, animal and environmental health in close relationship with food and water safety and security. In an era of climate change, resource depletion, land degradation, food insecurity and development challenges, an integrative approach is needed to ensure sustainable health. This concept strongly applies to all chronic inflammatory diseases, because of a strong scientific basis of epigenetic regulation of the disease genes with the influence of changing environment. Human health, animal health, plant health, healthy air, water and earth, food safety & security are integrative components of the "**One Health**" concept.

F) A fully integrated **World Allergy and Asthma Network** should be established with all national asthma centers and already established networks, alliances, societies, academies aiming at worldwide allergy surveillance, strategy development and education. Prioritization of allergies should take place more and more in the EU, United Nations, WHO and national political agendas.

G) **A multidisciplinary and scientific approach is essential**. 40 scientists and clinicians from all around the world and various fields of allergy and related disciplines gathered under the sponsorship of the Christine Kühne - Center for Allergy Research and Education (CK-CARE) for the 2nd Global Allergy Forum from 16 to 19 June 2013 in Davos, Switzerland. The participants representing major academies and societies formed working groups to discuss the actual most urgent problems. Role of environment, mechanisms of allergic inflammation and protection, allergy prevention, allergy diagnosis and therapy as well as education was particularly focused.

In a parallel action that brings together political bodies and scientists, representatives of the European Academy of Allergy and Clinical Immunology, the European Respiratory Society, the International Primary Care Respiratory Group, the Polish Allergy Society, the WHO Global Alliance against Chronic Respiratory Diseases, and the European Federation of Allergy and Airway Diseases Patients' Associations were invited by the Polish Minister of Health to convene and discuss how to prevent and control chronic respiratory diseases in children on Sept 20–21, 2011. These conclusions were adopted during an interministerial conference of the 27 EU Member States,on Dec 2, 2011.

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The European Academy of Allergy and Clinical Immunology (EAACI) is a non-profit organization active in the field of allergic and immunologic diseases such as asthma, rhinitis, eczema, occupational allergy, food and drug allergy and anaphylaxis. Its scope covers both basic science and clinical medicine.

Since its establishment in 1956, EAACI has grown to become the largest medical association in Europe in the field of allergy and clinical immunology. Its membership currently includes nearly 7800 members from 121 countries, representing academicians, clinicians, and allied health professionals. In addition, EAACI includes 47 National Allergy Societies as members.

EAACI's mission is to provide the most efficient platform for scientific communication and education in the field of allergy and immunology, ultimately striving to ease the lives of patients suffering from these diseases. EAACI is regarded as the **primary source of expertise** in Europe for all aspects of allergy.

EAACI's activities

- Fostering science through dedicated platforms Annual Congress, Focused Meetings, Guidelines and Position Papers
- Educating professionals (Allergy Schools; CME system; knowledge examination in allergy and clinical Immunology; Research and Clinical Fellowships)
- Disseminating knowledge through EAACI Journals (Allergy, Pediatric Allergy Immunology, Clinical and Translational Allergy, EAACI Newletter) and online communication platforms
- Advocating change and raising awareness among the European Union's decision makers about the importance of allergy and clinical immunology and the opportunities to prevent and treat allergies through *Public Campaigns* and *Public Declarations*

Allergy today is a global public health concern of pandemic proportions and it requires immediate action. The European Academy of Allergy and Clinical Immunology called on all worldwide leaders to develop the "Global Atlas of Allergy".

The "Atlas" was written by an international group of 183 World leaders in allergy and asthma research and is aimed to highlight the burden of allergic diseases worldwide as of sufficient magnitude to warrant recognition as a priority in national health strategies; to describe mechanisms and risk factors and evaluate the best ways to prevent and control allergic diseases, to provide guidance on how to overcome barriers ahead such as poverty, poor education and infrastructure, low public health priority due to the importance of other illnesses and the lack of good worldwide valid epidemiologic data; to ensure that cost-effective management approaches, which have been proven to reduce morbidity and mortality are available to as many persons as possible with allergic diseases worldwide; to establish an action plan to manage resources for allergic diseases prevention and to prioritise funding for allergy research.

A "Global Allergy Fight Strategy" should be developed, involving all stakeholders and targeting all aspects from optimal patient care and access to diagnosis and essential drug to innovative pathways for disease prevention and future drug discovery.

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